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The Horse's Mouth

With the impact of science on society become so immediate, there is growing pressure from both within and without the scientific community for scientists themselves to speak up on happenings outside the laboratory. The basis for the demand is clear. In matters of morality most of us are utilitarians: we hold a man responsible for the consequences of his acts irrespective of whether what happened is what he intended. For us, good will is not enough. But any attempt by scientists to assume broader responsibilities raises two hard questions—first, who is to do the talking? and second, what is to be talked about? Unfortunately, not all combinations of possible spokesmen and possible topics are equally innocent.

In the question of who is to do the talking, it is helpful to divide the possible spokesmen into two groups. In one group are individuals who claim to do no more than speak for themselves, although a viewpoint may gain weight from the fact that the person expressing it has made an important contribution to science. In the other group are voluntary associations of scientists which may speak as associations through official representatives or through committees.

In the question of what is to be talked about, it is helpful to divide the possible topics also into two groups. In the one group are topics which bear on the professional interests of scientists and which affect only indirectly the interests of the general public—for example, teaching salaries, opportunities for research, and academic freedom. In the other group are topics which bear more directly on the social consequences of new scientific findings and which may involve judgments about the adequacy of the findings as well as about public policy concerning their use—for example, tolerance limits for food additives and the level of radiation exposure to be permitted workers in atomic facilities.

The two groups of possible spokesmen and two groups of possible topics combine in several ways without raising any problem unique to the impact of science on society. Thus, it is fair for an individual scientist to express his views on the social consequences of a particular finding, since this is but a special case of any citizen's right to express his views on matters of general concern. And, it is fair for an association to seek to advance the professional interests of its members, since this does no violence to practices generally accepted as proper to associations. But difficulties do arise when a scientific association speaks out on the social consequences of new findings. Although any association suffers the embarrassment of how to handle a minority voice, this last combination faces a special danger.

The danger lies in the possible introduction of an authoritarian note into the competition of scientific ideas. Of course, there is such a thing as informed opinion. Every informed person knows that Aristotle's physics and biology have been superseded by the physics of Newton and the biology of Darwin, which in turn have given place in various ways to newer ideas. But in the forefront of research, which is the area that bears most immediately on public issues, diversity of opinion rather than unity is what often characterizes the scientific enterprise. If there is such a thing as the party in power, then there is also the loyal opposition—loyal in its adherence to the principle that the way to settle differences of opinion is by the study of nature, and opposed in its interpretation of the present data.—J.T.

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Psychopharmacologic Drugs

Harold E. Himwich

The last few years have seen the increasing use of a new group of drugs effective for overactive psychotic patients and presenting interesting and important differences from procedures and drugs previously employed in the management of individuals with such behavioral disorders. In fact, in order to give an appropriate name to these drugs, it was necessary to invent a nomenclature. Many terms, all emphasizing one or another aspect of the actions of these drugs, have been devised. The one most frequently used is *tranquilizer,* indicating a sedative or calming effect without enforcement of sleep. Others are *ataraxic* (*1*), denoting peace of mind, and *neuroleptic* and *neuroplegic,* indicating diminutions in the intensity of nerve function. This group of drugs, however, may be regarded as an advance guard of a long-awaited pharmacologic attack not limited only to hyperactive disturbed patients, but also to be directed against other types of behavioral disorders. To this division of drugs the term *psychotropic* (*2*), or action on the mind, has been applied. *Neuropharmacologic* refers to the branch of pharmacology to which these drugs belong. The title *psychopharmacologic drug* (*3, 4*), possesses certain advantages, for it indicates a medicine which influences the mind by affecting its morphologic substrate, the brain.

The chief usefulness of the new drugs, which at present lies in the field of psychiatry, is being extended into the many medical and surgical specialties. It is true that a drug not only changes favorably the malfunction of the organ for which it is intended but also acts, perhaps to a lesser extent, on the entire body. Either indirectly, by their influence on the brain, or by their influence on the peripheral nerves, the new drugs exert potent effects on the viscera of the body, including the gastrointestinal tract and the cardiorespiratory system and the endocrine glands.

But the impact of these new drugs has extended far beyond their immediate practical use in the management of disease. They are also employed by the clinical investigator who is seeking to unravel the tangled skein of abnormal behavior as well as by the psychologist who delves into intricacies of accepted normal patterns. Neurochemists and neurophysiologists have taken advantage of the tranquilizers to use them as tools in their investigations and meanwhile are uncovering their physiological actions in the brain and elsewhere in the body. These studies, made on man and lower animals, permit an analysis of the structure and function of the central nervous system, impossible before. Not that the methods are new, but the tranquilization resulting from the application of these drugs has not been previously observed. Perhaps most important, the new drugs may aid in the production of a desirable change in our culture and remove mental disease from the field of mysticism and superstition. They may convince the public that mental disease is not a thing to be ashamed of and that it should be placed in the same category as any other disease which can be treated by medical means.

Clinical Aspects

At this time it is hardly necessary to emphasize the magnitude of the problem of mental disease. The title of Gorman's recent book, *Every Other Bed* (*5*), is suggested by the fact that half of the sickbeds in our country are occupied by mental patients. The financial requirements for the maintenance of these hospitals are correspondingly great. The money comes chiefly out of the taxpayers' pockets. Only comparatively wealthy families can bear the cost of maintaining one of their members in a private institution.

The growing population of our mental hospitals indicates that advances made prior to the advent of new drugs were not adequate to cope with the problem of mental disease. Much was left to be desired, therefore, from the therapeutic viewpoint. Psychoanalysis is a better weapon in the management of the neuroses than of the psychoses. Electroshock is a comparatively severe procedure, for electrodes are applied to the temples of the patient and a brief, measured current is passed through his brain. The patient becomes momentarily unconscious and undergoes a convulsion. Electroshock greatly benefits patients with depression and is of value in the management of excessively hyperactive patients to maintain the uneasy status quo which characterizes hospitals not using tranquilizing drugs. Insulin hypoglycemia appears to be more effective than electroshock for certain types of schizophrenia but requires highly trained physicians and is costly. In insulin hypoglycemia, the patients receive doses of insulin large enough to reduce the level of sugar in the blood. The brain is thus deprived of its chief foodstuff, and the patient sinks into coma. Another method for treating the distraught patient is to stupefy or anesthetize him with an adequate dose of one of the barbiturate drugs.

Though the immediate situation can thus be met, it is not necessarily followed by improvement in behavior. With the tranquilizing drugs, however, the patient is improved without significant interruption of consciousness—a highly desirable goal in the successful therapeutic process. Even if his manic excitement is extreme and if he must be given a correspondingly large dose, which renders him

The author is director of the research division of Galesburg State Research Hospital, Galesburg, Ill.

sleepy, he can be easily awakened and in general can go on with his prescribed hospital activities. With the new drugs, more patients have been returned to society from the state hospitals than with any previous therapeutic regime. We therefore seem to be entering a new era in the treatment of mental disease, and it remains to be seen how far this advance will take us.

Schizophrenia

What are the mental disorders to which these new drugs are applied? The field of mental disease is complex. It is not a case of a single mental disease. On the contrary, there are many categories, and each one includes several varieties. Schizophrenia is the chief disorder met with in our psychotic population. We do not know the cause of schizophrenia, and this makes it necessary to limit our attack on it to empirical methods. But this is not unusual in the history of medicine, for the majority of therapeutic successes were produced on an empirical basis; witness the use of quinine long before the plasmodium of malaria was discovered.

Because the origin of schizophrenia is not known, that disease must be characterized chiefly by its symptoms. These are many and varied and, in general, may be divided into four types, which may change and merge into each other. The clinical picture is therefore not constant, and at different times the signs of one or another of these four types predominate. One of the characteristics of schizophrenia is emotional blunting, and this is a prominent change in the *simple* type. The psychiatrist is quick to observe the diagnostic paucity of facial expression and regards it as an outward lack of emotional expression or affect. Some individuals with inadequate personalities, who lose one job after another, belong to this group of patients. Sometimes the patient wears a silly and inappropriate grin. If such a patient, like Mr. M. on one of our wards, exihibit restless hyperactivity, at least that aspect of his disorder can be corrected by a tranquilizing drug.

An abnormality of the thought process is another characteristic of schizophrenia and is developed most highly in the *hebephrenic* type. Sentences spoken may have meaning for the patient but to others are neither coherent nor logical. In the most serious distortion of the thought process, the spoken word ceases to assume sentence form and is called "word salad." Mrs. H. replies to all questions with the unintelligible statement "16-21 telephone pole." That phrase includes her usual conversational limits. After receiving a new experimental tranquilizer, she informed us, in well constructed sentences, that she was born in a small village, consisting of six homes, and that her home was situated near a telephone pole numbered 16-21.

Delusions or false ideas and hallucinations, or false sensory impressions, are characteristic of the *paranoid* type. Unlike the utterances of the hebephrenic, which cannot be comprehended by the physician, those of the paranoid patient are readily understood but reveal lack of relation to reality. Mrs. G., one of the patients in our hospital, has suffered intensely for a long time from well-developed delusions of a gigantic "crime ring" which is out to get her, even penetrating into the confines of the Galesburg State Research Hospital. Recently, when she was receiving a test drug, a new serenity was observed in her demeanor. When asked about the "crime ring," she smiled, made a deprecating gesture with her hand, and said it did not bother her any more. In fact, she doubted whether it existed. This is an evident amelioration and was maintained as long as the patient remained on this medication.

In general, hallucinations, which also occur in mental disease other than schizophrenia, yield more readily to these drugs than do delusions. Mrs. S. has placed cotton plugs in her ears for many years to shut out the voices that were so hostile and were giving her such a bad time. During a period in which she was receiving one of the test drugs, she came in for an interview without the cotton plugs in her ears. The voices no longer tormented her, or at least not to the same extent as previously.

In the *catatonic* type of schizophrenia there are marked distortions of motor activity. Stupor is one aspect, and whether with or without stupor, posturing and the assumption and maintenance of bizarre positions and mannerisms are observed. After one has raised the arm of such a patient, the patient may keep his arm up for a long time. When he walks he may change his direction by turning at right angles only. A catatonic may also go into a furor, a period of wild overactivity, and become highly destructive.

Here we come to a very important use of tranquilizing drugs—namely, a calming action which is being applied to various kinds of destructive patients and not only to combative schizophrenics. Taking chlorpromazine and reserpine as examples, we find two different kinds of pharmacologic actions characteristic of this group of drugs. The first, which counteracts such symptoms of schizophrenia as dissociated thought, hallucinations, and delusions, has just been described. The second drug effect is of a different type and causes a general toning down of emotional reactions and physical activity. If the ability to correct the thought processes of the hebephrenic and the paranoid patients is regarded as a specific antipsychotic power of chlorpromazine and reserpine, then the use of these drugs to combat excessive activity may be considered a nonspecific result. As has been pointed out by Barsa, these two results do not necessarily occur together; either may be observed without the other (*6*). The calming action of the drugs cuts across the diagnostic categories of mental disease, for it is employed in all types of overactive patients, irrespective of the diagnosis. It can even be given to an individual who has no behavioral abnormalities, and in such a normal person a reduction of activity and a diminution in the response to environmental stimuli will be noted.

Use with Hyperactive Patients

It must be remembered that patients with psychoses are sent to psychiatric hospitals most often because they display behavior which is not socially compatible. Psychotics who can carry on outside the hospital gates are not necessarily sent to such institutions. When a patient presents behavioral disorders that menace the life and limb of other individuals as well as his own, it is essential that he enter a hospital where he can be properly treated.

Types of hyperactive patients who secure benefits from this sedative influence include the manic, whose disorder is chiefly that of mood or affect, which is greatly elevated; the schizoaffective, in whom abnormal elation is associated with deterioration of mental abilities; and the patient with a toxic psychosis, as in delirium tremens. These patients have their hyperactivity and abnormally increased initiative reduced to more reasonable levels so that they cease to wear themselves out and are no longer a trial to the ward attendants and their fellow-patients. This is a tremendous advantage for hospitals with highly disturbed patients. Isolation rooms, where a dangerous patient was formerly incarcerated, are no longer required. Mechanical restraints, sedative wet packs, electroshock, and deep barbiturate medication are prescribed only infrequently. As a result,

many of these patients can now be liberated from physical restraints as well as from the psychological constraints of a locked ward. The ward doors have been opened, and privileges have been given to many patients, permitting them to traverse hospital halls and attend various therapeutic activities—recreational, occupational, and industrial. Thus, treatments have not only been made more humane, with greater benefit to the patient, but have also effected improvement in the staff morale of the mental institutions. A hospital atmosphere is being established in state institutions to an extent that was not previously possible. One now feels that a mental hospital is not a place for the expedient management of an intolerable situation but rather a treatment center for the amelioration of disease, like hospitals devoted to other kinds of disorders.

One patient will receive most benefit from a certain tranquilizing agent, and a second from another. This is not the place to compare the therapeutic efficacy of the various tranquilizers, especially in such an early state of their development, but it is obvious that some produce a deeper sedative action than others. Each of the accepted tranquilizing drugs, when given in adaquate dosage, is of aid to disturbed patients, but our experience (*7*) with hyperactive patients has been widest with chlorpromazine (*8*) and reserpine (*9*), drugs which have profound sedative or calming actions. But there is no way to foretell which drug will be most effective for a given patient, and therefore the psychiatrist should be prepared to employ any one in an emergency. Some, like azacyclonol (*7, 10*), can bring about better social adjustment, so that the atmosphere on the ward becomes friendlier, especially among patients who are only moderately disturbed. The choice of a tranquilizing drug must be decided empirically; the best one for a given patient can be found only by the process of elimination.

The most dramatic improvements are observed in the first acute attack or in the chronic patient who has developed an acute exacerbation of his disorder. At our hospital, however, tranquilizing drugs have also been found to exert marked benefit in patients with schizophrenia of long duration—that is, chronic schizophrenia, as documented in the case histories presented above. But the improvements were mainly seen in patients with obvious active schizophrenic processes—those who had hallucinations and delusions or who were hyperactive, agitated, and tense. Blocked, retarded, and apathetic schizophrenics are more difficult to help. This greater intractability of the so-called "burned-out" patients, who have survived a more active phase of their disorder and who seem free of schizophrenic symptoms and excessive physical activity, is also observed with previous methods of treating deteriorated, passive schizophrenics.

Similarly, senile patients who are irritable, quarrelsome, and apprehensive show greater improvements than patients who exhibit negativism, apathy, and withdrawal. It would appear that tranquilizing drugs are less valuable for the senile patient who does not display signs of agitation. For the same reason, depressions not accompanied by anxiety and tension are less apt to be ameliorated by a psychopharmacologic agent. The treatment of the passive patient is therefore more difficult. In individuals with hypertension, apparently free from behavioral abnormalities, the use of these drugs may lead to a worsening of the mental condition if the profound sadness of a depression is induced.

Psychoneuroses

Mental diseases milder than the psychoses are the psychoneuroses or neuroses, and in some forms of these disorders tranquilizing drugs are of value. In contradistinction to the psychotic patient, the neurotic acts, by and large, as if reality has the same meaning for him as for most people. He is not subjected to persecution by a "crime ring" and does not have other bizarre experiences. He suffers, however, from great anxiety, which may not be readily identified with any particular object. Yet this anxiety is expressed in bodily symptoms: palpitation, breathlessness, weakness of limbs, tremors and pains that plague him. For that reason, in some patients, the anxiety is associated with a particular organ: the heart, the lungs, or the stomach. Neurotics who must be active in order to escape their disturbing fears are usually not helped by tranquilizers. In contrast, those with internal tensions, who cannot sleep despite use of such sedative drugs as the barbiturates, often gain relief from a psychopharmacologic agent.

For the "Normal" Population

These drugs also exhibit decided usefulness for the members of our so-called normal population who are subjected to intolerable stress. A businessman with a demanding and unreasonable supervisor or a woman with insufficient funds to run her home according to her ideal standard can gradually build up an emotional impasse so that perspective is lost, as the darker side of the situation is increasingly magnified, until a state of panic may develop. Restoration to a more objective evaluation of the situation may be secured by psychotherapeutic discussions with a physician, and an important action of tranquilizing drugs is to render the patient more receptive to other kinds of therapy. In fact, at times a psychopharmacologic drug may be essential for a successful psychiatric interview. Ephemeral disturbances—for example, the anxiety and tension aroused by an impending surgical operation—can be pleasantly dissipated by a small dose of a tranquilizing agent.

Side Reactions

I have not mentioned the matter of occasional undesirable side reactions of the new drugs (*11*). In the first place, the drugs cause much less inconvenience than the mental disorder of the psychotic patient. Some patients can be managed by a temporary reduction of dosage—for example, a patient who exhibits an excessive fall of blood pressure. Others can be treated by a drug which counteracts the undesirable changes; a tremor of the hands resembling that of Parkinsonism can be relieved by an anti-Parkinson drug. Patients with brain injury are more likely to exhibit a convulsion than those with an intact organ (*12*). The production of lactation and menstrual changes by chlorpromazine and reserpine and the power of the latter to impair libido in the male are subjects for research. Fortunately, serious complications occur only rarely. A small number of patients develop jaundice, a sign of liver involvement. In some instances there may be a reduction of white blood cells. A failure in the formation of these cells is dangerous because it diminishes the resistance of the body to disease. But, on the whole, the treatment of thousands of psychotic patients with the new drugs has been relatively safe, because most are resistant to these side effects. This resistance, however, does not apply to neurotic patients, who seem more sensitive to side reactions and even on comparatively low dosage complain of fatigue, prostration, dizziness, and nausea.

It is apparent, then, that state hospitals have been placed on a much better basis by the use of the tranquilizing drugs, especially in the management of highly disturbed patients. The same, however, can-

not be said of psychiatrists whose private practice is concerned chiefly with neurotic patients. But it is also true that many patients who were formerly sent to a mental institution can now be treated outside the hospital gates. Some psychotic individuals can continue to lead productive lives and need not go to a psychiatric hospital at all. During the acute phase, they may be controlled by tranquilizing drugs in a general hospital and later may be maintained outside the hospital on appropriate doses of these medicines. On the other hand, apathetic psychotics who are not in conflict socially but who are rather withdrawn, inactive, and without signs of agitation, usually cannot be raised to a higher adaptive level. They are still the despair of the psychiatrist. In evaluating the present clinical position of the psychopharmacologic drugs, it must be understood that the production of tranquilization, though a desirable end in itself, also aids other forms of therapy. A potent factor in the successful treatment of a patient with disorganized or disturbed behavior is a satisfactory relationship with a psychiatrist, and an important result of tranquilization is the facilitation of such a beneficial relationship.

Neurohormonal Changes Caused by Reserpine and Chlorpromazine

A lead for the pharmacologic attack on schizophrenia comes from a study of indole-containing substances. Not only serotonin but also the tranquilizer reserpine and the psychotomimetic lysergic acid diethylamide (LSD) contain the indole nucleus (see Fig. 1). The idea that indoles are associated with schizophrenia is not new (*13*). In a similar vein, suggestions have been made that serotonin plays a part in brain function (*14*). A clinical analysis of this problem became available in 1954 with the paper of Hoffer, Osmond, and Smythies (*15*). These experimenters knew that an adrenaline solution which had become pink after standing in the light for a long period of time had exerted psychotomimetic effects. They also drank a solution containing impure adrenochrome and succumbed to its influence to the extent of revealing schizophreniclike changes in their behavior. They therefore thought that the pink solution might contain a breakdown product of adrenaline, similar to adrenochrome in being indolic in character, and pointed out that some indole-containing substances affect behavior adversely. Thus, again we have the suggestion of the pathogenic importance of indole-containing substances. However, it should be pointed out that not all such compounds evoke aberrant behavior. Moreover, drugs with entirely different chemical structures—for example, hashish—are psychotomimetic in action. Nevertheless, it is instructive to examine the effects of serotonin.

The experiments of Welsh (*16*) showed that in the clam *Venus mercenaria* the accelerator nerve of the heart, for which serotonin is the chemical mediator, is inhibited by LSD. Gaddum and Hameed (*17*) have demonstrated the antagonism of LSD to the peripheral action of serotonin in mammals and wondered whether or not this antagonism might not also apply in the brain. Woolley and Shaw (*18*) made the bold hypothesis that LSD produced behavioral abnormalities by interfering with the physiological actions of serotonin in the brain. According to these investigators, LSD is enough like serotonin to be taken up by the serotonin receptors in the brain, yet is different to the extent that LSD fails to evoke serotonin effects.

The Rockefeller workers used the lock-

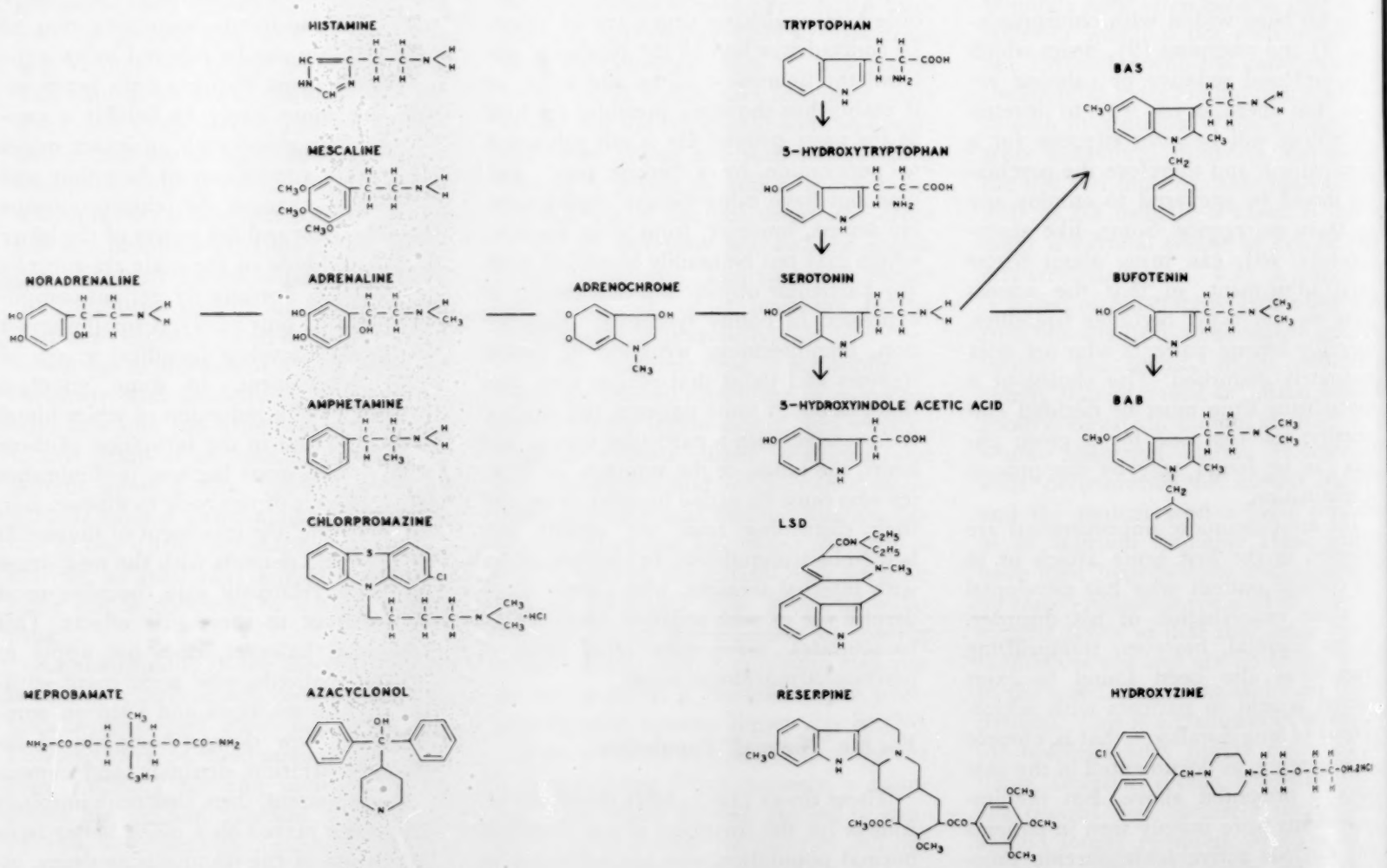


Fig. 1. Structural formulas of some neurohormones, psychotomimetic agents, and tranquilizing drugs.

and-key analogy: LSD could be introduced into the same lock as serotonin but, in contrast, could not be used to turn the lock. This suggested, of course, that mental aberrations are produced by an inadequate amount of serotonin at its site of action, the receptors with which serotonin combines. But it is also possible that there may be an excessive concentration of serotonin in some forms of mental disease, and in a later paper these workers showed that LSD could also act like serotonin and, for example, increase the effects of that brain hormone to raise the blood pressure of anesthetized dogs (*19*). Costa (*20*), in our laboratory, found that LSD can either diminish or increase the effects of serotonin, depending upon its concentration. The serotonin-evoked contraction of a rat uterus is antagonized by LSD in a solution containing 1.0 microgram per liter but is facilitated by that psychotomimetic agent when its concentration is reduced to 0.2 microgram per liter or less. The latter result suggests that an excess of serotonin, rather than a deficiency, is a disturbing factor in mental disease. In the present status of these investigations it is not possible to decide between these two alternatives. In fact, both may be correct, but each may apply to different kinds of abnormalities.

Reserpine, which is so valuable in the management of combative destructive patients, reduces the concentration of serotonin in the body (*21, 22*). Furthermore, only those *Rauwolfia* alkaloids which are tranquilizers have this depleting action in the stores of serotonin (*23*). According to one explanation, the competition between the drug and serotonin displaces the latter from its receptors and, as a result, the neurohormone is eliminated from the depots in the brain and other parts of the body. Restoration of serotonin to normal levels is protracted. After a single dose of reserpine was injected into a rabbit, the brain serotonin was depressed to 10 percent of normal within 4 hours and remained at this low level for 36 hours, after which it rose slowly over a period of 6 days before premedication values were attained (*22*). Following the administration of reserpine, the concentration of that drug in the brain increased rapidly to a brief maximum, but in contrast to the long-enduring depletion of serotonin (*24*), reserpine diminished speedily and was practically undetectable in the brain in about 4 hours. These results with reserpine, obtained by a fluorometric method, are in agreement with the concept that reserpine produces pharmacologic effects indirectly by its influence upon the serotonin content of the brain. But other observations (*25*) with a more sensitive technique, employing isotopically labeled reserpine, disclosed that the radioactive material is extractable from the brain *as reserpine* up to 48 hours after its injection. The long presence of reserpine in the brain does not necessarily exclude the theory that reserpine acts through an indirect mechanism that involves serotonin, but it is in accord with the idea that reserpine acts as such.

Additional evidence that reserpine releases serotonin has been adduced by Valcourt (*26*), who observed two groups of patients, one schizophrenic and the other mentally defective, at the Galesburg State Research Hospital. A significantly increased urinary excretion of 5-hydroxyindoleacetic acid occurred during the first day of the administration of 4 milligrams of reserpine. Apparently, when serotonin does not attain its binding site, it is rendered vulnerable to the amine oxidase enzyme and is metabolized to form 5-hydroxyindoleacetic acid (Fig. 1).

Even if it is proved that serotonin is important to the function of the mind, its action is not a simple one, for that hormone may serve in other ways. Because serotonin can cause smooth muscle—the type of muscle in the walls of arteries and of viscera—to contract, it is thought to be a factor in the production of high blood pressure and in the motility of the gastrointestinal tract. Only 1 percent of the serotonin content of the body is found in the brain (*27*). Most of it occurs in the spleen and especially in the gastrointestinal tract containing the specialized cells of the enterochromaffin system, which secrete serotonin (*28*). A tumor of these cells, called malignant carcinoid, is associated with abnormally high levels of blood serotonin and with an increased excretion of its metabolic product, 5-hydroxyindoleacetic acid, in the urine (*29*). Behavioral changes are absent, perhaps because of the relative impermeability of the brain to serotonin (*30*).

The similarities between serotonin, an indole amine, and the catechol amines, noradrenaline and adrenaline, are important. These similarities are not limited to their areas of distribution in the brain (Figs. 2, 3), which in general reveal high concentrations in various subcortical areas and low ones in the cerebral cortex and cerebellum (*31, 32*), nor are their resemblances confined to their chemical structures (Fig. 1), which dis-

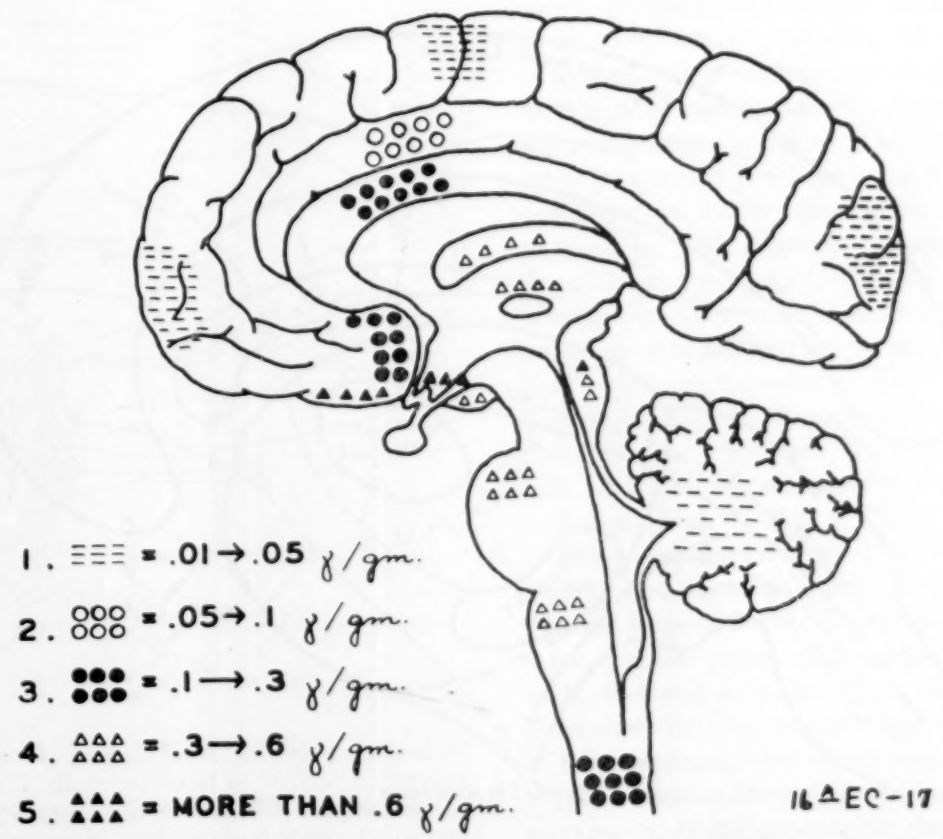
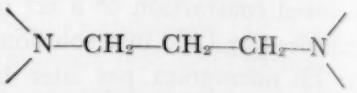


Fig. 2. Serotonin content of the human brain. The areas with the highest concentration of serotonin, an indole amine, include the hypothalamus. A lower level is observed in the mammillary bodies, fornix, thalamus, and medulla oblongata. Serotonin is found in the cingulate gyrus, hippocampus, and amygdaloid nucleus in greater concentrations than in the neocortex or cerebellum, which contain the least amounts. [Costa and Aprison (*32*)]

close that adrenaline can be oxidized to form an indole amine, adrenochrome, and that the latter, plus the appropriate side chain, yields serotonin.

Most striking is the discovery that reserpine exerts an action on noradrenaline and adrenaline similar to that previously disclosed for serotonin—that is, it empties their stores wherever they occur in the body. Even more significant is the observation (*33*) that the curve for the time relationships for the release of these substances from the brain and the reestablishment to premedication values follow each other closely. Though the results are not the same when different methods for the determination of no adrenaline are used, yet in general the is agreement in the rapid release (3 from the brain and the slow return normal values. It is obvious, then, th the releases of these amines are close associated phenomena. Either the amine combine with the same receptor, thoug not necessarily with the same prosthet group, or the discharge of one amin initiates the liberation of the other.

One action of reserpine, therefore, in volves closely allied substances whic may be included in the term *biogen amines*. Can such a conception be ap plied to chlorpromazine? An examina tion of the structure of chlorpromazine (Fig. 1) reveals two chief portions, th phenothiazine nucleus and a side chai



Suggestions arise from an examinatio of both portions of the chlorpromazine molecule. If the phenothiazine nucleus portion is depicted in three dimensions instead of two, it closely resembles th indole nucleus, as observed in serotonin as well as in reserpine. It does not seem however, that chlorpromazine acts in th same manner as reserpine, for chlorpro mazine does not empty the depots o serotonin and the catechol amines. An other lead comes from the examinatio of the side chain, which is contained in many successful phenothiazine deriva tives (*35*). As has been pointed out by Gyermek and others (*35, 36*), the same side chain occurs repeatedly in substances which depress the effects of amines. It must not be forgotten that the pheno thiazines belong to the group of antihis taminic drugs and can usually inhibit actions evoked by histamine (Fig. 1). In fact, such a side chain will interfere with the effects of other biogenic amines, in cluding noradrenaline, adrenaline, and serotonin. Chlorpromazine shares with these biogenic amines a side chain of similar construction, and perhaps chlor promazine attaches itself to the same binding site as do these amines.

If such a generalized action may be attributed to chlorpromazine, the study of the chemical substrates of behavior becomes even broader than the indole viewpoint suggested by the pharmaco logic action of reserpine and renders every biogenic amine a fit subject for investigation in the field of behavior. But even these broad possibilities do not ac count for the chemical aspects of tran quilizers not included in the reserpine and chlorpromazine groups. As an ex

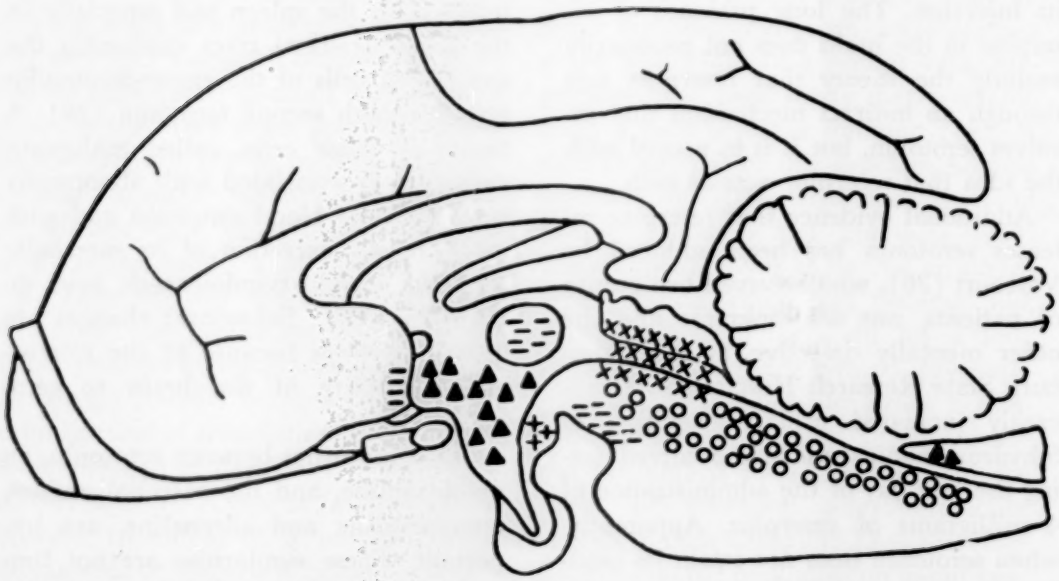


Fig. 3. Medial sagittal section of a dog's brain, showing the distribution of noradrenaline in micrograms per gram of fresh tissue: ▲, 1.0 μg/g; +, > 0.4 and < 1.0 μg/g; ○, > 0.3 and < 0.4 μg/g; −, > 0.2 and <0.3 μg/g. In the dog brain, the catechol amines, noradrenaline and adrenaline, are at their highest concentration in the hypothalamus; then, in decreasing amounts, in the mammillary bodies and the reticular formation. Still lower concentrations are observed in the neocortex and cerebellum. [Vogt, *J. Physiol. (London) (31)*]

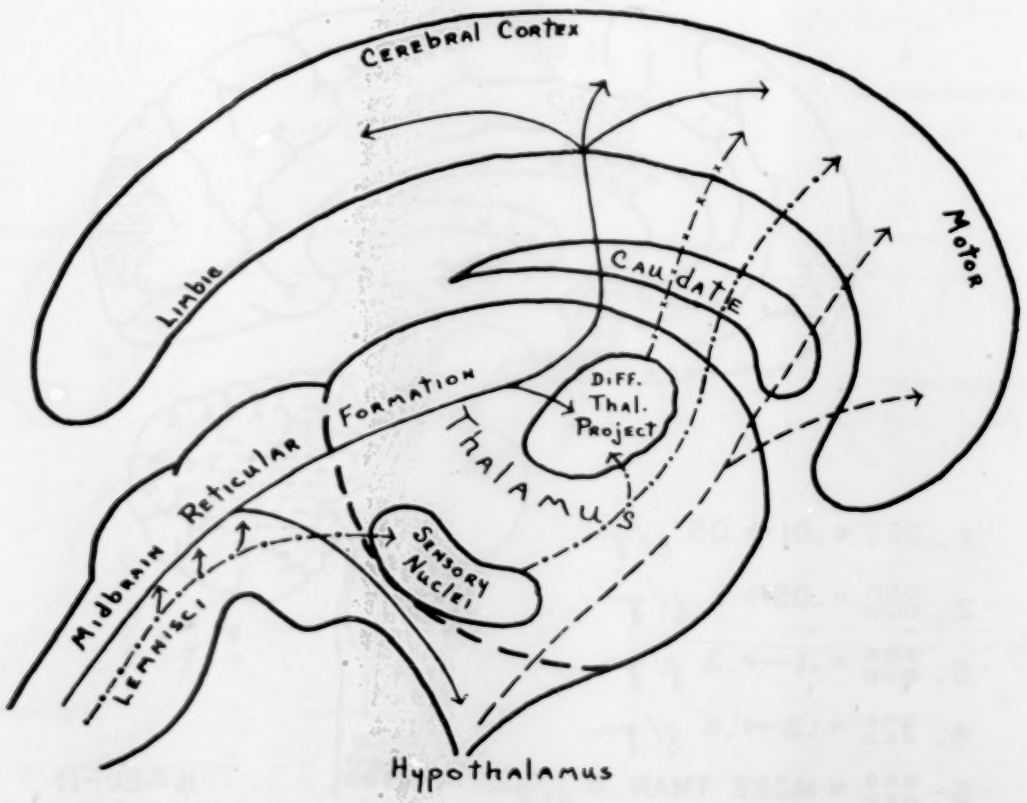


Fig. 4. Mesodiencephalic activating system. Stimulation of the organism evokes impulses which travel by way of the lemnisci to the thalamic sensory nuclei and then to cortical sensory areas. The lemnisci send collateral nerve fibers to the midbrain reticular formation, and by these fibers impulses advance in the reticular formation to the diffuse thalamic projections and arouse the cerebral cortex. Collaterals bearing stimuli from the midbrain reticular formation pass to the hypothalamus, which in turn sends impulses to the cerebral cortex. [Himwich, *J. Nervous Mental Disease* (*3*)]

ample, we may cite the experiments of Costa, who showed that the peripheral effects of serotonin were blocked not only by reserpine and chlorpromazine but also by azacyclonol (20). Moreover, meprobamate, hydroxyzine, benactyzine, and many other drugs, each with different chemical constitutions, are effective in various degrees against one mental condition or another. Until the chemical advances catch up with the clinical advances, some of the manifestations can be followed in the form of changes in nerve function.

Neurohormonal Equilibrium

Marrazzi and Hart (*37*) propose a theory, depending upon an equilibrium between various hormones, that may account for results with diverse types of tranquilizers. They contrast the stimulating effects of acetylcholine, a chemical mediator of the nerve impulse across the synapse, the junction between two nerves, with the inhibiting action of adrenaline, amphetamine, mescaline, and LSD. The latter group depresses and may even stop the transmission of the nerve impulse from one nerve to the next. Marrazzi and Hart also report that tranquilizing drugs —reserpine, chlorpromazine, and azacyclonol—prevent the inhibitory effect of mescaline on the transmission of the nerve impulse. They regard the signs of psychosis as release phenomena, results of the removal of normal restraints. Their experimental work also discloses that the depressant influence of serotonin is more potent than that of adrenaline, amphetamine, mescaline, or LSD. They therefore suggest that mental derangement is caused by an imbalance between such inhibitory substances as serotonin and the chemical transmitter of the nervous impulse, acetylcholine.

It is known that acetylcholine is active in the function of several cerebral areas, including the mesodiencephalic activating system, which is discussed in the succeeding section of this article (*38*). In a way, this conception is somewhat like that of Pfeiffer and Jenney, that an increase of acetylcholine may exert an antischizophrenic effect, for raised concentrations of that neurohormone should antagonize the action of serotonin to block the transmission of the nerve impulse (*39*). But it is not impossible that a dearth of acetylcholine is associated with one type of abnormal behavior, perhaps psychosis, and that an excess of acetylcholine is an accompaniment of another type, neurosis. Jacobsen (*40*) has suggested that the action of Benactyzine to block acetylcholine may serve a beneficial effect in disturbances associated with supernormal concentrations of acetylcholine (*41*). Benactyzine exerts little influence on schizophrenic patients but has been termed an antiphobic drug because it is effective against abnormal fears and reduces the emotional reactivity to stress.

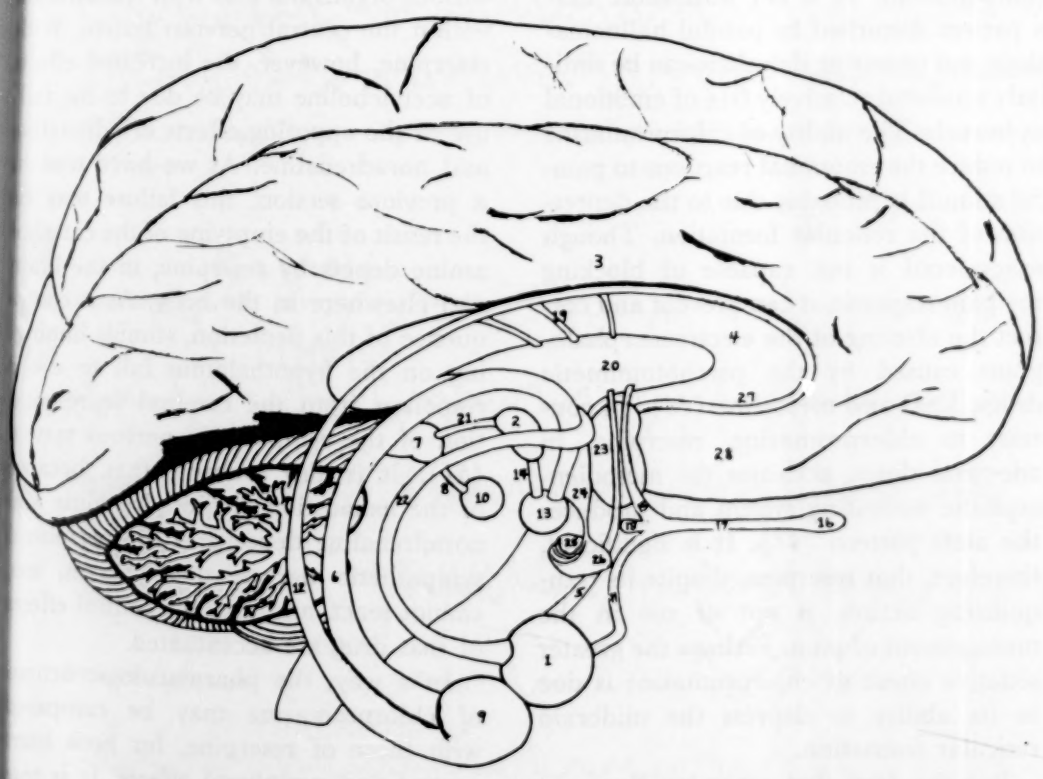


Fig. 5. Semidiagrammatic section of human brain. 1, amygdala; 2, anterior nucleus of thalamus; 3, cingulate gyrus; 4, corpus callosum; 5, diagonal band of Broca; 6, fornix; 7, habenula, a nucleus of the thalamus; 8, habenulopeduncular tract; 9, hippocampus; 10, interpeduncular nucleus; 11, lateral olfactory stria; 12, longitudinal stria; 13, mammillary body; 14, mammillothalamic tract; 15, medial olfactory stria; 16, olfactory bulb; 17, olfactory tract; 18, olfactory tubercle; 19, perforating fibers; 20, septum pellucidum; 21, stria medularis; 22, stria terminalis; 23, subcallosal gyrus; 24, hypothalamus; 25, posterior pituitary gland; 26, anterior pituitary gland; 27, caudate nuclei in depth of brain; 28, septal region. [Adapted from "Physiology and Pharmacology of Emotion," *Scope* 4, 1 (1955)]

Anatomic Sites of Action

Differences between the pharmacologic actions of depressant drugs like the barbiturates and of the tranquilizers are mentioned above in the section on "clinical aspects." An important cause for the diverse effects of these two different kinds of drugs is disclosed by an examination of their sites of action. It is well known that every drug may affect many parts of the body, but it must also be emphasized that some areas, usually the important ones for the therapeutic results, are more susceptible than others. Take, for example, the barbiturates, which in general act most strongly on the later-developed parts of the brain—the cortex of the cerebral hemispheres—and least so on the more primitive medulla oblongata, containing vital centers for the control of heart rate, respiration, and blood pressure. Because of their pronounced effects on the cerebral cortex, barbiturates depress functions of the cortical regions concerned with the analyzing mechanisms of vision, audition, and other perceptive functions—the fine coordination of motor movements as well as thought and memory. Though the tranquilizers also affect functions ascribed chiefly to the cerebral cortex, their most potent actions are exerted on the subcortical structures regarded as parts of the anatomic substrate of emotion: the midbrain reticular formation, the hypothalamus, and the components of the rhinencephalon (Figs. 4, 5).

The viewpoint expressed in this article is that the tranquilizing drugs pick out, for their main sites of action, these three cerebral areas, all connected with each other and with the cortex. It would seem that the visceral functions, related to the emotions, were correlated chiefly by the reticular formation in the lower vertebrates. It is also probable that, later in the evolutionary process, other centers in the hypothalamus and especially in the rhinencephalon took over much of the emotional aspect of behavior.

A more detailed description of the

midbrain reticular formation reveals that it is an ancient cerebral area, well developed even in the Amphibia, as has been shown by the work of Herrick on the tiger salamander (*42*). In that animal, the midbrain reticular formation probably serves as an important integrating mechanism, coordinating muscular and visceral activities in accordance with the sensory information evoked by changes in the environment. We owe the elucidation of the basic physiology of the reticular formation in mammals and primates to Moruzzi, Magoun, and their students (*43*). These workers showed that the midbrain reticular formation acts in conjunction with the diffuse thalamic projections (Fig. 4), as ascribed by Jasper (*44*). Thus, the phyletically older midbrain reticular formation is united functionally with the later-developed diffuse thalamic cortical projections, and the two together form the mesodiencephalic activating system (*38*). This does not mean that the mesodiencephalic activating system is independent of the rest of the brain. On the contrary, its midbrain reticular component probably receives a varying number of stimuli by way of collateral nerve fibers from the lemnisci (Fig. 4). There are therefore two parallel systems. One carries information by way of the lemnisci and the paths of the sensory thalamic nuclei to the cortex, where the messages are analyzed for specific information on the kind of stimulus, its point of application, and similar relationships to the organism. In the other system, the mesodiencephalic activating system, nerve impulses ascend in the reticular formation to the thalamic nuclei, which then send other impulses to the cortex by way of the diffuse thalamic paths. The mesodiencephalic activating system thus affords the emotional cloak which accompanies some kinds of stimulation of the body.

The parts played by the hypothalamus and the rhinencephalon will be considered below, but with this background we can proceed with the psychopharmacologic analysis of the functions of the mesodiencephalic activating system, which has been shown to be sensitive to members of the reserpine group of drugs, to chlorpromazine and other phenothiazine derivatives, and to azacyclonol. A clue to the effect of these drugs on this system is afforded by the electroencephalograph, for stimulation and inhibition are each accompanied by characteristic brain-wave patterns. Those associated with inhibition of the reticular formation are also observed, with rest or light dozing in the human being or animal, and are shown on the left side of Fig. 6*A*. They are characterized by high-amplitude slow waves and spindles of rapid waves. The latter are most prominent in the motor cortex, as is seen in records obtained from a rabbit. This type of activity continues until the animal is exposed to auditory, tactile, or painful stimuli, when rapid low-amplitude waves, particularly in the cortex, appear, while a slower regular rhythm develops in the hippocampus. On the right side of Fig. 6*A* is seen such an alerting or arousal pattern (*3, 45*). On the other hand, when chlorpromazine is given, the reticular formation is blocked and no longer shows the alerting response (Fig. 6*B*). This inhibition of the reticular formation does not prevent impulses evoked by a painful stimulus from traversing the lemnisci (Fig. 4), and awareness is thus achieved by way of the cortical mechanisms, but the severity of the associated distressing emotional accompaniment of the stimulus is greatly mitigated.

A clinical example is seen in the use of chlorpromazine for the treatment of the intractable pain associated with inoperable cancer. Surely the patient is aware of the pain, but it has been largely robbed of its harrowing emotional accompaniment. It is not impossible that a patient disturbed by painful hallucinations and upsetting delusions can be similarly rendered relatively free of emotional upheavals. The ability of chlorpromazine to reduce the emotional reactions to painful stimuli is probably due to the depression of the reticular formation. Though azacyclonol is not capable of blocking the pain response, it can prevent and correct the alerting of the electroencephalogram caused by the psychotomimetic drugs, LSD and mescaline (*46*). In contrast to chlorpromazine, reserpine, in adequate doses, activates the mesodiencephalic activating system and produces the alert pattern (*47*). It is significant, therefore, that reserpine, despite its tranquilizing action, is not of use in the management of pain. Perhaps the greater sedative effect of chlorpromazine is due to its ability to depress the midbrain reticular formation.

But the fact that reserpine does not inhibit the mesodiencephalic activating system indicates that there are other centers important for tranquilization. We therefore turn next to the consideration of the hypothalamus, which is known to be a part of the brain containing patterns for coordinating visceral functions, increases of blood pressure, heart rate, and respiration in order to support muscular activity. This integration of visceral and muscular activities is especially essential in emergency situations, originally referred to by Cannon as the "fight or flight" reactions (*48*). This part of the brain, therefore, organizes the visceral manifestations which are overactive in disturbed patients. It would seem probable that the depression of this mechanism acts to mitigate this type of overactivity. The earliest research done on reserpine and chlorpromazine indicated that these drugs inhibited hypothalamic structures, particularly those of the posterior hypothalamic nuclei which regulate the sympathetic nerves to the viscera and blood vessels (*49*).

The action of reserpine can be explained in part by a depression of the sympathetic representation in the hypothalamus (*50*), which leaves parasympathetic activity unopposed and thus accounts for the fall in heart rate, drop in blood pressure, constriction of pupils, and the increased intestinal motility frequently observed in patients receiving that drug. These physiological changes are signs of acetylcholine activity. Acetylcholine is not only associated with the chemical transmission of the nerve impulse in parasympathetic nerves to the various organs but also with transmission within the central nervous system. With reserpine, however, the increased effects of acetylcholine may be due to the failure of the opposing effects of adrenaline and noradrenaline. As we have seen in a previous section, this failure may be the result of the emptying of the catecholamine depots by reserpine, in the brain and elsewhere in the body. As a consequence of this depletion, stimuli impinging on the hypothalamus fail to evoke responses from the cerebral representation of the sympathetic nervous system (*51*). It is also probable that, because of the exhaustion of the adrenaline and noradrenaline deposits in the peripheral sympathetic nerves, these nerves, too, cannot react, and thus the central effects of that drug are accentuated.

In a way, the pharmacologic actions of chlorpromazine may be compared with those of reserpine, for both exert central and peripheral effects. It is true that both drugs inhibit the hypothalamus, but chlorpromazine also depresses peripheral sympathetic nerve centers which help to regulate blood pressure, and this is a second reason for the observed decreases of arterial pressure. But chlorpromazine also exerts a similar impairment on peripheral parasympathetic

nerves which usually slow heart rate, and therefore in patients receiving chlorpromazine the heart rate is characteristically rapid. Both peripheral results may be ascribed to interference with the action of acetylcholine in the transmission of the nerve impulse and therefore may be compared with the central operation of chlorpromazine to block the reticular formation (*52*).

Pathfinding Experiments

The discussion on the parts of the brain affected by chlorpromazine and reserpine will now be extended to include those which were highlighted by the pathfinding experiments of Klüver and Bucy (*53*). These workers removed the temporal lobes of monkeys, thereby changing these difficult creatures into remarkably tame animals. These primates also exhibited increased oral and sexual proclivities. Objects of all kinds were repeatedly introduced into the mouths of the animals being tested, and males, especially, attempted sexual intercourse frequently, whether or not the animal chosen for these relations was of the appropriate sex or even of the same species.

The temporal lobe includes some structures belonging to the rhinencephalon, which was first regarded as a unified system by Papez (*54*), in accordance with the schema presented semidiagrammatically in Fig. 5. When the hippocampus is stimulated it gives rise to impulses which initiate the Papez circle. These impulses are transmitted from the hippocampus (No. 9, Fig. 5), through the fornix (No. 6), to the mammillary bodies of the hypothalamus (No. 13). From that area they continue to the anterior thalamic nuclei (No. 2) and attain the cortex of the brain in the cingulate gyrus (No. 3). The functional circle is completed in fibers leaving the cingulate gyrus and returning to the hippocampus.

Again the phyletic point of view is enlightening. When the first air-breathing vertebrates—the amphibians and especially the reptiles—left the oceans for the land, they developed areas of the brain important for smell, the olfactory bulb (No. 16) and the olfactory tract (No. 17). The olfactory tubercle (No. 18), which receives impulses from the midbrain reticular formation, supplies an indirect connection between the latter and Papez' circle. The term *rhinen-*

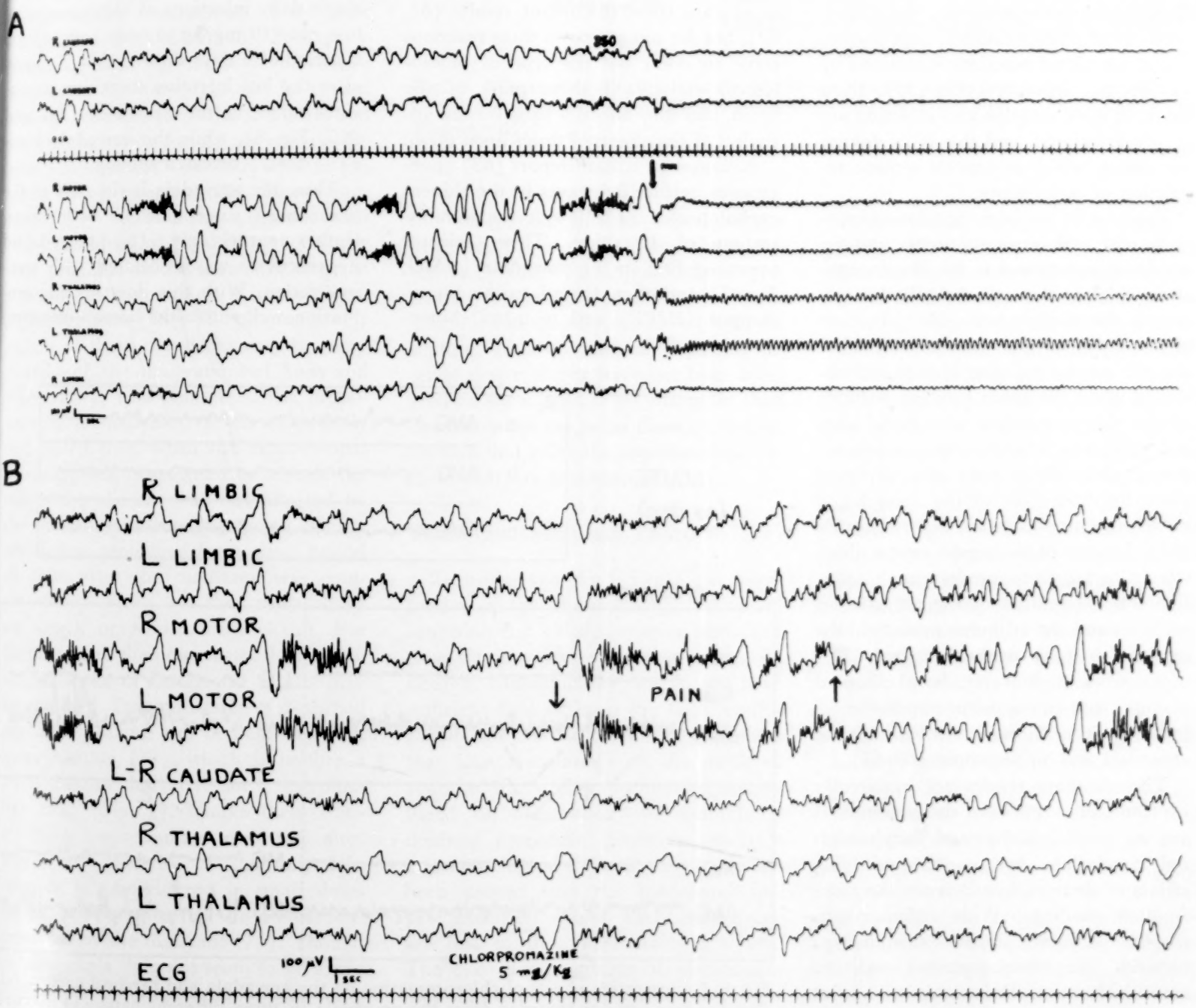


Fig. 6. Alert pattern evoked by pain and prevented by chlorpromazine. (*A*) Bilateral leads are taken from various cerebral structures: on right side, electroencephalographic control pattern of resting rabbit; on left side, the effects of pinching rabbit's leg. (*B*) Change produced by chlorpromazine (5 mg/kg) in electroencephalographic pattern in response to pain. Note the absence of the alerting reaction to pain. [Himwich, *J. Nervous Mental Disease* (*3*)]

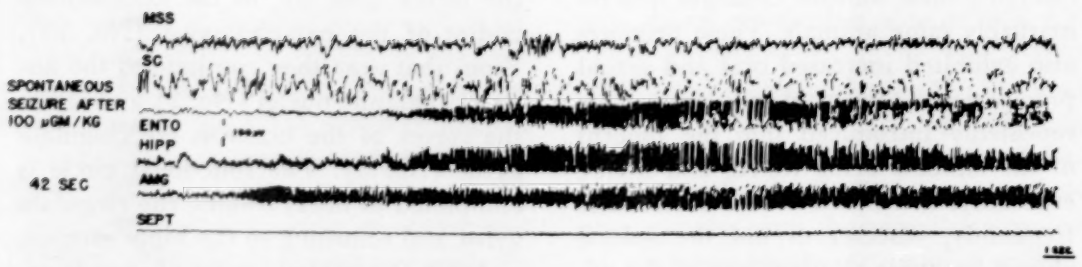


Fig. 7. Effect of reserpine (0.1 mg/kg) on brain waves; records of spontaneous rhinencephalic seizures initiated in the amygdala. [Killam and Killam, *Brain Mechanisms and Drug Action* (*63*)]

cephalon originates in the primarily olfactory functions of the bulb and of some of the amygdaloid nuclei (No. 1). These structures are connected, in turn, to others which have been adapted in higher animals to emotional activities. These include the remainder of the amygdaloid and septal nuclei (No. 28). Finally, the latter areas contact Papez' circle in the hippocampus, and awareness of emotional reactions is attained by way of the cingulate gyrus (*55*). Even today, in man, emotion and olfaction are closely associated, and this is so despite our mores, which in general require restriction of body odors.

The part of the brain concerned especially with emotional experience and the one least understood is the rhinencephalon, which is also called the limbic system or the visceral brain (*56*). It must be noted that not only tranquilization but also the reverse reaction of rage was observed when the more forward portions of the rhinencephalon—the septal area and olfactory tubercle—were removed, and similar effects were also reported after the extirpation of the amygdaloid nuclei, the hippocampus, and the fornix (*57*). Lesions of the septal region alone were also found to produce rage (*58*). Bilateral extirpation of the amygdaloid complex and the adjacent pyriform lobe rendered animals easily disturbed (*59*). Many workers, however, have observed placidity and emotional unresponsiveness following the bilateral removal of the amygdala and hippocampus (*60, 61*).

Though these results are apparently contradictory, at present the consensus is veering towards Klüver and Bucy's original conclusions because the pacifying effects of these extirpations are the more frequent findings. With either result, these experiments disclose relationships between the rhinencephalon and the emotional state. From this viewpoint both observations are useful, and in that case the nature of the response may depend on other factors—for example, the immediate social environment, whether or not it is hostile, and whether the animal is being provoked or treated in a friendly fashion. The general reaction characteristic of the animal is also important, for the effects of the operation may be superimposed on an excitable animal, easily aroused, or on a calm and phlegmatic one. Analyses have been made to explain these discordant results (*61, 62*), but for our purposes these reactions serve to point out the type of physiological activity of these parts of the brain, and they afford a basis for the appraisal of the effects of drugs upon them.

Killam and Killam report (*63*) spontaneous, seizurelike waves in the rhinencephalon of a cat following the administration of reserpine. These seizures appeared first in the amygdala (*AMG*, Fig. 7) and then spread to the hippocampus (*HIPP*) and to other rhinencephalic structures, including the entorhinal cortex (*ENTO*) and septum (*SEPT*). However, the neocortex, (*MSS* and *SC*) remained free of such abnormalities. Furthermore, Sigg and Schneider noted that electrically evoked, seizurelike waves in the amygdala were facilitated and prolonged by reserpine without necessarily involving neocortical areas (*64*).

Preston's observations (*65*) with chlorpromazine are similar in some respects to those of the Killams with reserpine, for he reports that the amygdaloid complex is readily stimulated by chlorpromazine at a time when the activity of the neocortex, including the motor cortex which regulates voluntary muscular movements, is unchanged. The electroencephalographic alterations evoked by single daily injections of chlorpromazine to a cat (10 mg/kg of body weight) for a period of 5 days showed that 20 hours after the last injection there was no obvious effect in the neocortex (*LG* and *MC*, Fig. 8), while the amygdaloid nuclei (*AMG*) revealed spiking.

Thus, the amygdala is the part of the brain most susceptible to both drugs. Rather surprisingly, this amygdaloid hyperactivity was associated with tranquilization. With this dose of chlorpromazine, well within the human therapeu-

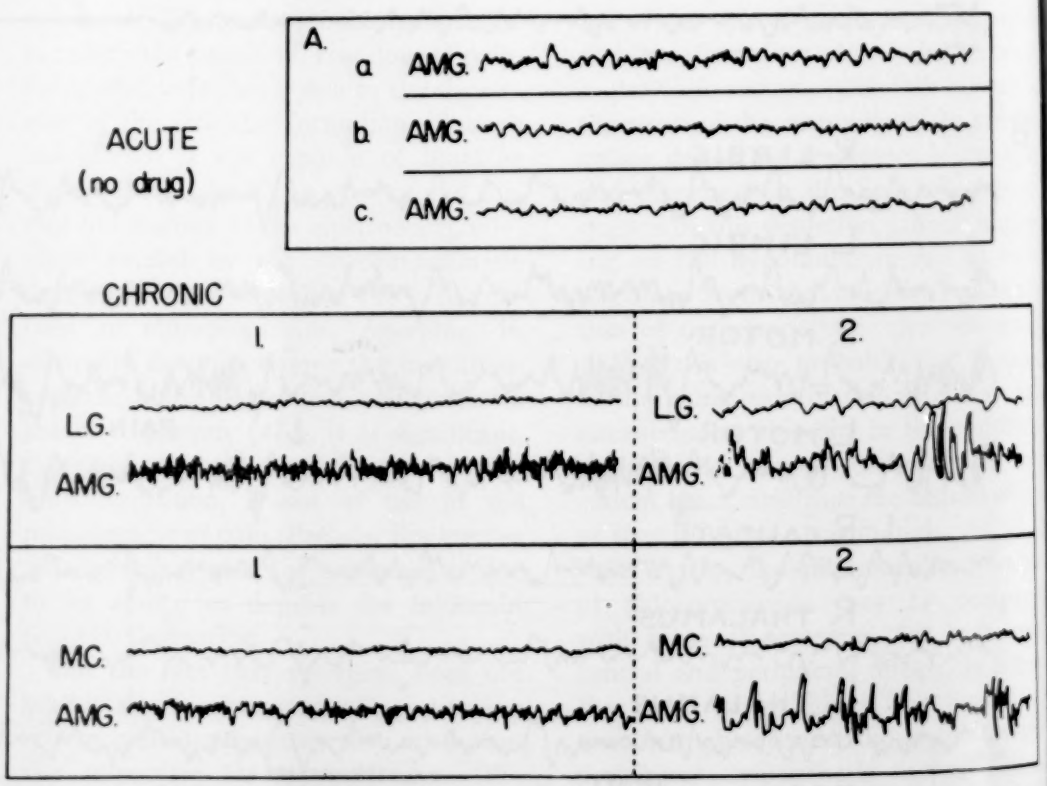


Fig. 8. Comparative effects of chlorpromazine on the amygdala and cerebral cortex. (*A*) Spontaneous activity recorded from the amygdala in three different cats: (1) Records from two cats after a single daily injection of chlorpromazine, 10 mg/kg, for 5 days; (2) spontaneous activity recorded at a later time in the same experiment after 10 mg/kg of chlorpromazine had been injected. Hyperactivity is present in amygdala but not in the neocortex. [Preston, *J. Pharmacol. Exptl. Therap.* (*65*)]

tic rage, a cat will not pounce upon a mouse placed in its cage but, instead, acts with apparent indifference. Though the convulsive brain waves disclosed in the amygdala were accompanied by a transformation in the behavior of the cat, overt signs of motor activity were not apparent in such animals. In general, it is known that the rhinencephalon is more easily excitable than is the neocortical mantle of the cerebral hemispheres (*66*). With larger doses of chlorpromazine (*65*), which however do not exceed those administered to badly disturbed patients (*67*), the electrical hyperactivity spreads from the amygdala (*AMG*, Fig. 9) to other rhinencephalic structures, the septum (*SEPT*) and the hippocampus (*HIPP*). But only when the disturbance extends to neocortical motor areas are the characteristic violent muscular contractions of a major epileptic seizure observed. Perhaps a similar process, the initiation of seizure activity in the amygdala and its spread through the rhinencephalic structures and then to the motor cortex, can explain the convulsive seizure sometimes seen in patients taking reserpine and chlorpromazine (*12*). Penfield has suggested that the phenomena of psychomotor epilepsy may originate in a seizure discharge in the amygdala spreading in the centrencephalic system (*68*). The pharmacologic effects of these two drugs may be compared with the observations of Andy and Akert (*69*), who stimulated the hippocampal formation of a cat electrically and noted that, when the hippocampal discharge was propagated to include the amygdala, the cat was not affected by the presence of the mouse, an apathy which was prolonged for a short period of time after the discharge was completed and which was then replaced by an attack upon the little victim. But there is more than one method by which similar kinds of behavioral results may be obtained. Tranquilization of disturbed psychotic patients can be achieved with meprobamate (*70*), which is neither a phenothiazine derivative nor a reserpine-like drug (Fig. 1). Unlike these tranquilizers, meprobamate does not alter brain wave activity of the amygdala when it is administered in small doses which, however, depress the undulations exhibited by the thalamus (*71*). Though the amygdala does not seem to be a site of activity for meprobamate, yet some portion of the rhinencephalon may be involved, as suggested by experiment with animals. Rats rendered savage by

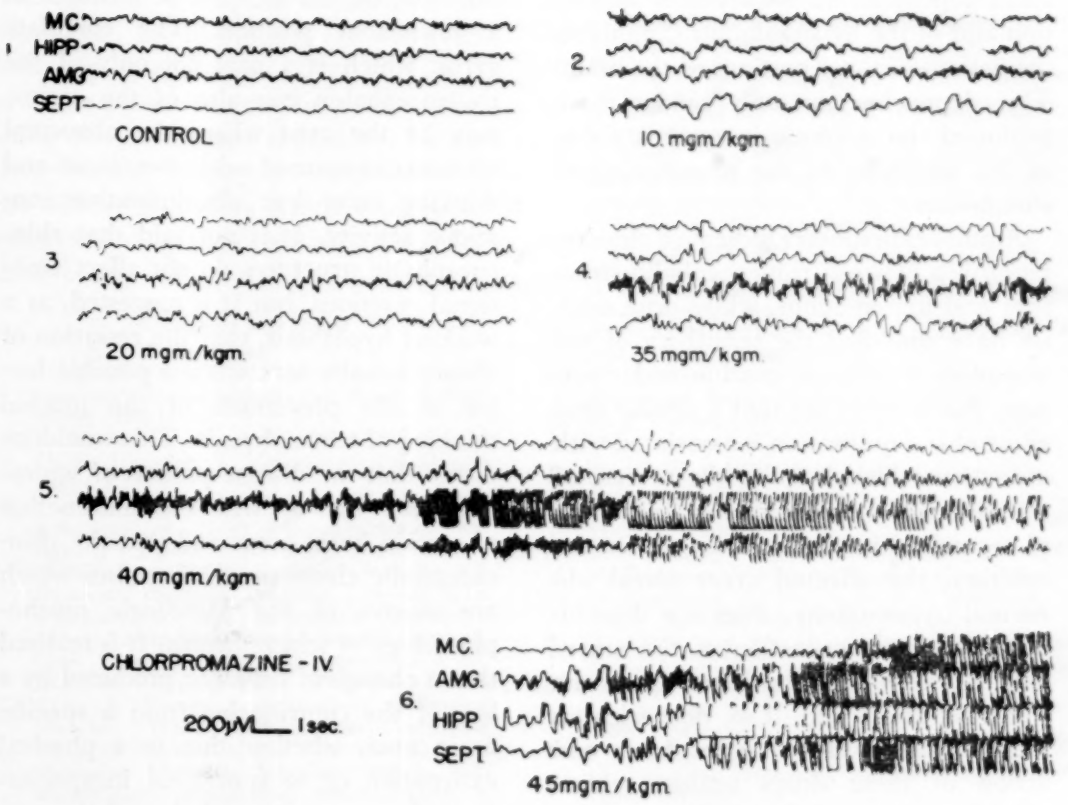


Fig. 9. Effects of gradual increases of chlorpromazine upon brain. Seizure spiking is initiated in amygdala and gradually spreads to other areas. [Preston, *J. Pharmacol. Exptl. Therap.* (*65*)]

the extirpation of their septal regions are restored to their preoperative behavior by that drug. Apparently meprobamate influenced a portion of the brain which is functionally associated with the septum. It is of more than passing interest that rats that have not been operated on show little or no change in their conduct when the same doses of meprobamate that calm the experimental animals (*72*) are administered.

Theory for Therapeutic Effects

To bridge the gap between our information of the pharmacologic actions of reserpine and chlorpromazine and their therapeutic results is a goal greatly to be desired. Unfortunately, we do not have sufficient data or even the basic neurophysiologic facts to do this. It is realized that such speculations on the mode of action of tranquilizers in man are largely based on observations of animals—a doubtful procedure. Moreover, there is a genuine logical difficulty, for it has not been proved that the behavioral improvements noted with use of these drugs are due to the pharmacologic effects. The two diverse groups of phenomena may be related to each other only by a common causative factor—namely, the drug. But it is useful to make the assumption that the medicines are causes of the clinical changes as a device to clarify our thinking in seeking indications for the direction of future research in the field of psychopharmacology.

In our analyses of the therapeutic results of reserpine and chlorpromazine, we found that they are of two different kinds: one is a calming of the individual and another is directed against schizophrenic manifestations. Can each of these two different clinical improvements be related to specific actions of the drugs? The decreased reactivity of tranquilized patients may be ascribed in part to the depletion of the catechol amines, the depletion depriving the organism of part of the mechanism of reactivity. Obviously, tension and anxiety, whether evoked by real or imaginary emergencies, will nevertheless mobilize the autonomic nervous system. Not only adrenaline and noradrenaline but also other hormones, including serotonin and acetylcholine, are probably released during threatening emergencies. Thus, in general, a pharmacologic action of these drugs is to remove part of the mobilization mechanism, and the beneficial results include tranquilization and decreases of anxiety and tension. Turning to the electrophysiological portion of this analysis, we find ourselves examining the parts of the brain which help to regulate the activity of the neurohormones. A neu-

ronal depression of the reticular formation and of the hypothalamus diminishes the actions of these portions of the brain. This depression can only render more profound the decrease in reactivity due to the emptying of the neurohormonal storehouses.

Animal experiments indicate a close relationship between rhinencephalic structure and the emotions, while drug studies have disclosed the sensitivity of the amygdala to chlorpromazine and reserpine. But here we see that a similar final effect of tranquilization is associated with an action which is quite the reverse of that seen in the hypothalamus. Inhibition of nerve function is not observed. On the contrary, the affected areas reveal abnormal hyperactivity. Does the drug-induced aberrant operation of the amygdala interfere with the functions of the rhinencephalon, and, if so, does such an interference afford a basis for the second action of these drugs against schizophrenic symptoms? It would seem that the normal contribution of the amygdala to the economy of the brain cannot continue when that structure is being subjected to seizures (*73*). Perhaps the rhinencephalic chain ceases to act physiologically because of the functional failure of the amygdaloid link—a failure which makes for a loss in a connection between the most primitive brain area (concerned with emotion), the midbrain reticular formation, and the later developed rhinencephalon.

The diminution in reactivity of the organism probably influences the quantity or intensity of the emotional impact on the cortex. But it is difficult to see how such an amelioration can change the quality of thought so that the dissociated "word salad" of the hebephrenic patient can become less incoherent, more logical and comprehensible. One can appreciate that a decrease in emotional intensity might mitigate the violence in the expression of hallucinatory and delusional material, but again it is more difficult to understand how such a mitigation can cause the correction of schizophrenic mentation. For that change, thinking must be altered in quality.

Though the various parts of the brain work together as a unit in a coordinated manner, we have seen that certain structures, both cortical and subcortical, are more involved than others in our emotional life. Similarly, as is pointed out by Bailey (*74*), some subcortical regions add a crude awareness, but for the discriminative contribution to that complex function, the cortex must be included in a prominent position. The cingulate gyrus, which is a part not only of the rhinencephalon but also of the cortex, may be the area where the abnormal elements concerned with awareness and thinking enter into discriminative conscious activity. It is not said that rhinencephalic structures do not affect emotional reactions, but it is suggested, as a working hypothesis, that the cessation of rhinencephalic function is a possible factor in the prevention of the morbid thinking of schizophrenia. This would indicate that the disease process of schizophrenia is tied up with the malfunction of certain brain areas and that the rhinencephalic circle carries impulses which are sources of the pathologic psychophysiology of schizophrenia. It is realized that a change of behavior produced by a loss of the contribution from a specific brain area, whether due to a physical extirpation or to functional incapacitation, does not prove that pathology in that area is the source of the disease. The removal of a part of the brain may interfere with the function of another region more directly concerned with the disease process. For example, an origin of the pathologic course may lie within the septal region, as is indicated by the work of Heath and his colleagues (*75*), or the warped emotional reactions may find their earlier expression in the midbrain reticular formation. But at least it can be said that the anatomic site sensitive to drug action bears a relationship to schizophrenia, because the functional diversion of that area may correct the symptomatology of the disorder.

Paths of Research

A review of the present pharmacologic data can serve to throw light on paths for future exploration. One series of observations has emphasized quantitative changes causing shifts in the neurohormonal balance, involving excesses or deficits of acetylcholine, adrenaline, noradrenaline, serotonin, or serotoninlike substances. Concentrations of serotonin in the brain can be increased by the administration of its precursor, 5-hydroxytryptophan, which provokes disturbances in the electroencephalogram and in the behavior of the rabbit (*76*) (Fig. 1). Apparently, 5-hydroxytryptophan enters the brain rapidly and, presumably, is transformed into serotonin. But that does not demonstrate that serotonin is excessive in hyperactive psychotic patients (*77*) or that their improvement is necessarily due to the decrease of serotonin in the brain. On the other hand, there is a recent suggestion that Marsilid, which increases the serotonin content of the brain, benefits depressed patients (*78*). Again, that does not prove that patients are depressed because of abnormally low levels of serotonin in the brain. But it must be admitted that this circumstantial evidence is of such interest that it calls for further investigation of these possibilities.

An experiment to throw light on this subject would be to determine the cerebral serotonin contents in the brains of psychotic patients and compare them with those of nonpsychotics. A start has been made. Costa and Aprison have demonstrated that serotonin is a normal constituent of the human brain just as it is of the brain of lower animals (*32*). However, it can be said conservatively that the suggestion of Woolley and Shaw (*18*) on the role of serotonin is an attractive one and that it has been useful in turning up new material (*79*). For example, Shaw and Woolley (*80*) have synthesized compounds which block serotonin, including BAB, the benzyl analog of bufotenin, and BAS, the benzyl analog of serotonin (Fig. 1). We have employed BAS in the treatment of schizophrenics on the possibility that it may exert a reserpinelike action (*79*). The salutary results on these psychotic patients were very encouraging, but the side reactions contraindicate the clinical use of BAS.

It is not justifiable, however, to separate the role of serotonin from that of the catechol amines, for both are affected simultaneously by reserpine and probably by other tranquilizing drugs. A strong point in favor of the catechol amines is that one of them, deoxyephedrine, is able to substitute for depleted catechol amines in the brain (*81*). Mice and monkeys, under the influence of reserpine and showing the depression, reduced mobility, and the hunched posture typically produced by that drug, are dramatically restored to apparently normal activity by deoxyephedrine. Another line of investigation is concerned more with qualitative changes in the neurohormones than with quantitative ones, and it implicates a metabolic factor in schizophrenia. This work cannot be reviewed here, but it involves the more rapid oxidation of adrenaline (*82*) or the production of abnormal oxidation products of that neurohormone (*83*). As a result of an abnormal enzyme system, the metab-

olism of adrenaline is perverted, and an aberrant metabolic product, which may be a pathogenic factor in schizophrenia, is formed (*84*).

At this time, when theories of schizophrenia are actively multiplying, it would seem that the two different aspects of quantitative and qualitative changes in the hormones are not mutually exclusive. One example is afforded by Hoffer, who suggests that there are two basic conditions for the production of schizophrenia—an increase in the concentration and activity of acetylcholine within the brain and an abnormal metabolic diversion of adrenaline to some aberrant indole compound (*85*).

The inclusion of electrical changes of brain areas in our field of research diversifies the problem still more. At the present state of development of psychopharmacology it is difficult to apply William of Occam's razor, for each successful drug seems to differ from the others. Perhaps when we know more, the attack will be simplified by a unitary hypothesis on the pharmacologic actions of these drugs. We are therefore left with a number of tempting speculations, and the judgment of the investigator will largely determine which one will be emphasized in his researches.

The fact that we have effective drugs will not stop the production of better ones. In that process, a guiding principle is concerned with a characteristic of the brain—the fact that it, more than any other organ, is sensitive to changes in the chemical structure of a drug (*86*). Illustrations may be drawn from the phenothiazine derivatives. Profound differences in the intensity of the therapeutic effects and the distribution of the side reactions (*35*) may be produced either by the replacement of the chlorine (Cl) atom of the nucleus with another chemical or by an alteration in the number of carbon atoms between the two nitrogen atoms (N) of the side chain. We are looking forward to the discovery of compounds of new chemical structures, to be used for types of patients who require not tranquilization but other kinds of therapeutic aid—for example, for the blocked and retarded individual who must be stimulated without an increase of hostility or an activation of hallucinations and delusions.

We have seen, however, that thus far in the field of psychopharmacology, practice has outstripped theory. Though we recognize that tranquilizers correct certain schizophrenic symptoms, there is less agreement on the mechanism by which the improvements are achieved. Whether or not drugs effect cures is a problem for the future. But the practical value of the advance should not be underestimated. It may be compared with the advent of insulin, which counteracts symptoms of diabetes without removing their cause.

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University of Arizona Radiocarbon Dates

Edward N. Wise and Dick Shutler, Jr.

The Carbon-14 Age Determination Laboratory of the University of Arizona is operated by the anthropology department under the direction of Emil W. Haury, with the technical supervision of one of us (E. N. W.). A steering committee of the university (*1*) was appointed to approve the acceptance of submitted samples, to assign them a relative priority, and to examine critically and approve for publication the dates obtained by the laboratory.

The work of the Carbon-14 Age Determination Laboratory is an integral part of the geochronology-dendrochronology program of the university. Students in this program obtain laboratory experience by observing all the chemical and physical operations performed during the dating of a sample.

The laboratory was constructed in 1953 with the aid of a grant from the Research Corporation. The solid-carbon method developed by Willard F. Libby and his co-workers (*2*) is used for dating samples. Trial runs were made in the spring of 1954, and the laboratory was ready for calibration and dating runs in 1955. The solid-carbon method has been retained, for the majority of our samples are not more than 20,000 years old, and we have not experienced the radioactive contamination reported by other radiocarbon-dating laboratories. Fallout from the Nevada atomic-weapon test site apparently passes to the north of our laboratory.

The elemental carbon is prepared in essentially the same manner as that described by Libby, except for a modification suggested by Ballario and his coworkers (*3*). The modification concerns the omission of the steps in which carbon dioxide is condensed with liquid nitrogen. In the combustion train, the traps cooled with liquid nitrogen are replaced by a two-stage absorption train containing ammonium hydroxide, which absorbs the carbon dioxide directly. A water aspirator is attached to the end of the train to remove unabsorbed gases, such as excess oxygen. After precipitation and purification of the sample as calcium carbonate, carbon dioxide is evolved by the addition of hydrochloric acid. The carbon dioxide is thoroughly dried and directly reduced to elemental carbon with magnesium turnings. The elimination of the steps in which liquid nitrogen is used speeds up the preparation of samples and simplifies the control of the chemical processes involved in absorption and reduction. No deleterious effect on samples due to the omission of the use of liquid nitrogen was noted.

The problem of smooth and continuous chemical reaction during the reduction step, which gave trouble during our trial runs, was solved by heating the magnesium turnings in the steel reduction tube under high vacuum for several

Dr. Wise is associate professor of chemistry at the University of Arizona, Tucson. Mr. Shutler is a research assistant in the department of anthropology and operating technician of the Carbon-14 Age Determination Laboratory at the University of Arizona.

minutes prior to the admission of the carbon dioxide. Reduction was then easily initiated by local heating of the reduction tube to a bright red heat with a gas-air torch, and reduction always proceeded smoothly to completion.

The dates of the samples we have measured are listed in Table 1 (*4*).

The statistical error is derived by the method described by Libby (*2*). The figures for standard deviation attached to the dates are in some instances larger than the purely statistical error. This adjustment was made to reflect more correctly our estimate of other factors involved in the precision of an assay. This follows the practice of other laboratories such as that at the University of Michigan (*5*). Possible errors resulting from the processing procedure and sample material have been adequately discussed elsewhere by Libby (*2*) and Crane (*5*).

References and Notes

1. The steering committee is composed of Emil W. Haury, chairman, Edwin B. Kurtz, John F. Lance, David L. Patrick, Terah L. Smiley, J. E. Treat, and Edward N. Wise.
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Table 1. Radiocarbon dates obtained on archeological samples by the black-carbon method. All ages are given in radiocarbon years before the present. The year of assay is given in parentheses below the radiocarbon age. Specific locations of the samples collected in Arizona are given by the archeological site survey system of the Arizona State Museum.

Description	Sample No.	Age
Naco mammoth site, Ariz. FF:9:1, Cochise County (*6*). Fragmented charcoal in clay matrix surrounding Columbian mammoth bones. The two samples were combined and measured. Collected by E. W. Haury *et al.*; submitted by E. W. Haury, University of Arizona.	A-9, A-10	9250 ± 300 (1957)
Point of Pines Ciénega site, Ariz. W:10: 112, No. 2, layer D-1, Graham County (*7*). Fragmented charcoal from hearth, pine-oak. Layer D is composed of moist, dense, dark gray clay. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-19	4310 ± 160 (1955)
Point of Pines Ciénega site, Ariz. W:10: 112, Graham County. Highly fragmented charcoal in matrix of bed D-1, over area 3 m in diameter. The two samples were combined and measured. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-21, A-22	3980 ± 160 (1956)
Point of Pines Ciénega site, Ariz. W:10: 112, No. 9, Graham County. Carbonaceous material, directly above bones in cremation 36. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-26	3280 ± 200 (1957)
Point of Pines Ciénega site, Ariz. W:10: 112, No. 10, pit 6, Graham County. Charred, waterlogged pine branch. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-27	3070 ± 150 (1956)
Point of Pines Ciénega site, Ariz. W:10: 112, Graham County. Finely divided carbonaceous material associated with cremations in pit 3, bed C-2. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-28	2515 ± 300 (1956)
Point of Pines Ciénega site, Ariz. W:10: 112, No. 6, Graham County. Scattered charcoal fragments in D-1 layer, which is composed of moist, dark gray clay. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-29	4400 ± 150 (1956)
Lehner mammoth site, Ariz. EE:12:1, No. 1, Cochise County. Charcoal fragments mixed with sand from hearth No. 2. Collected by W. W. Wasley, University of Arizona; submitted by E. W. Haury.	A-30	8330 ± 450 (1956)
Lehner mammoth site, Ariz. EE:12:1, test No. 1, G17-G18, Cochise County. Carbonaceous material from black swamp soil layer above hearths, bone bed, and artifacts. Collected by W. W. Wasley; submitted by E. W. Haury.	A-31	6877 ± 450 6356 ± 450 (1956)
Lehner mammoth site, Ariz. EE:12:1, Cochise County. Charcoal fragments mixed with sand from hearth No. 2. Collected by W. W. Wasley; submitted by E. W. Haury.	A-32	7022 ± 450 (1956)
Lehner mammoth site, Ariz. EE:12:1, test No. 1, G17-G18, Cochise County. Carbonaceous material from black swamp soil above hearths, bone bed, and artifacts. Collected by W. W. Wasley; submitted by E. W. Haury.	A-33	7133 ± 350 (1956)
Lehner mammoth site, Ariz. EE:12:1, Cochise County. Charcoal and sand collected from hearth No. 1, 15 cm below black swamp soil. Collected by W. W. Wasley; submitted by E. W. Haury.	A-34	7205 ± 450 (1956)
Lehner mammoth site, Ariz. EE:12:1, Cochise County. Charcoal and sand collected from hearth No. 2, sample 4. Collected by W. W. Wasley; submitted by E. W. Haury.	A-40a A-40b	12,000 ± 450 10,900 ± 450 (1957)
Stick figurine site, NA5686, surface features 7 and 11, Coconino County, Ariz. Reeds, south side of Grand Canyon, about 4 mi from El Tovar Hotel in Cremation Canyon. Collected and submitted by Douglas W. Schwartz, University of Kentucky.	A-47	3100 ± 110 (1957)
Point of Pines Ciénega site, Ariz. W:10: 112, Graham County. Charcoal from pit 7, cremation 42. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-48	2150 ± 200 (1956)
Point of Pines Ciénega site, Ariz. W:10: 112, Graham County. Wood, rotten and wet, from bed C-3, the deposit in which pit 8 was cut. Sample A-53 was a re-run of sample A-49. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-49 A-53	2610 ± 200 2080 ± 200 (1956)
Point of Pines Ciénega site, Ariz. W:10: 112, Graham County. Charred wood, wet, material from pit 8. Sample A-52 was a re-run of sample A-50. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-50 A-52	3250 ± 200 3025 ± 200
Point of Pines Ciénega site, Ariz. W:10: 112, Graham County. Wood, rotten and wet, from bed C-3, the deposit in which pit 8 was cut. Collected by E. W. Haury *et al.*; submitted by E. W. Haury.	A-51	3380 ± 200 (1956)
Cedar from ship of Maarko Sestios. It is thought that the ship sank off the Island of Grand Congloue, near Marseille, France, about middle of second century before Christ. Submitted by Ferdinand L. Lallemand, archeologist at the Office français de Recherches sous Marines, Marseille, France.	A-66	2295 ± 110 (1957)
Double Adobe site, Ariz. FF:10:1, Cochise County. Charred wood from trench No. 2, east end, in river sand, in association with artifacts of the Sulphur Spring stage. Collected and submitted by E. B. Sayles, Arizona State Museum.	A-67	8200 ± 260 (1957)

Description	Sample No.	Age
Arizona EE:12:2, Cochise County. Charcoal, on San Pedro River about ¼ mile south of Hereford, Fort Huachucha Road, in erosion channel with artifacts tentatively identified with Chiricahua stage of Cochise culture. Collected by E. B. Sayles and Ernst Antevs; submitted by E. B. Sayles.	A-68	2850 ± 200 (1957)
Arizona EE:8:13, Cochise County. Sample from Murray Springs, about 1 mi west of Lewis Spring on San Pedro River, collected from heavily carbonaceous earth, about 500 ft northeast of an old ranch house at the forks of drainage, about 3 ft below the surface; the sample was overlain by fine silt in which Cochise-type artifacts occur. Overlies clay containing elephant bones (exposed in main drainage). Collected and submitted by E. B. Sayles.	A-69	8250 ± 200
Arizona CC:12:4, Cochise County. Carbonaceous material collected on San Simon Creek about ¼ mi north of the railroad bridge east of San Simon in erosion channel; probably Chiricahua stage. Collected by Ernst Antevs and E. B. Sayles; submitted by E. B. Sayles.	A-70	7000 ± 260 (1957)
Arizona EE:2:30, test 1, pit 1, Santa Cruz County. Charcoal, Matty Canyon, San Pedro stage, Cochise culture. Collected by Dick Shutler, Jr., and Alexander J. Lindsay; submitted by E. W. Haury.	A-74	1950 ± 200 (1957)

Horatio Hackett Newman, Pioneer in Human Genetics

Following the rediscovery of Mendel's principles in 1900, the science of genetics grew rapidly. Several species of plant and animal proved very early to be especially favorable for study. Among these were the fruit fly, *Drosophila melanogaster,* and corn, *Zea mays.* Very soon a solid foundation was laid for the development of the genetics of all plant and animal species, including the human species.

Developing simultaneously with this young science of genetics was Horatio Hackett Newman. Born in Alabama in 1875 and showing very early an interest in biology, he could hardly help becoming excited about the wonders of genetics that were then being rapidly revealed. By 1905 he had received his doctor's degree in zoology from the University of Chicago. After several years of teaching zoology at the University of Michigan and later at the University of Texas, he returned to the University of Chicago to become a member of its faculty. Newman, F. R. Lillie, and C. M. Child formed a triumvirate that gained or maintained for the zoology department of the University of Chicago a national and international reputation of first rank.

Very early in his career in zoology Newman developed an interest in plural births. He studied and published extensively on the embryological phenomenon of armadillos, in which all the members of each litter of four or six, depending upon the species, are invariably of the same sex and are invariably developed from a single fertilized egg. As time went on Newman gradually shifted his interest to human plural births, not so much because they interested him as a subject per se as because he recognized in them a powerful natural tool with which to evaluate the relative contribution of variations in heredity and environment to the occurrence of observed variations in human characteristics—especially mental characteristics.

Newman published six books and numerous articles. Particularly widely used in colleges and universities throughout the United States, and to some extent in foreign countries, was his book entitled *Evolution, Genetics and Eugenics.* Most outstanding, however, was his book, or monograph, called *Twins,* which he published in 1937 in collaboration with his University of Chicago colleagues Frank N. Freeman and Karl J. Holzinger. This book is a study of the psychology and heredity of about 50 sets of identical and 50 sets of fraternal twins, reared together, and of 21 sets of twins reared apart from infancy or early childhood. It is a study which has probably been quoted more often than any other in connection with the inheritance of human mental variations.

Newman was unusually modest and retiring. As a result of this he did not compete well. He was not interested in details if they did not contribute to broad principles. Yet, he was exceptionally tolerant of those who, in his opinion, picked pebbles and lacked interest in, or were incapable of contributing to, the building of castles. Following his retirement, in 1940, from the University of Chicago, he lived a quiet life at Clearwater, Florida, until the time of his death, in the summer of 1957.

Newman was one of the outstanding pioneers in the development of the science of human genetics in America and, therefore, throughout the world.

HERLUF H. STRANDSKOV
Department of Zoology,
University of Chicago, Chicago, Illinois

News of Science

Controlled Fusion

In response to the report that news of British control of the fusion reaction is being suppressed [*Science* **126**, 1281 (20 Dec. 1957)], Lewis L. Strauss, chairman of the Atomic Energy Commission, released the following statement from Paris, where he was attending the NATO Conference:

"A report to the effect that the United Kingdom Atomic Energy Authority has suppressed announcement of success in control of the fusion reaction at my request is completely false.

"Research on this problem has been carried on in both countries independently for a number of years. In 1953 the United States greatly accelerated its research program on which we had been spending less than a half-million dollars a year and are currently spending an amount many times as large and, indeed, as much as the research teams have called for.

"Since 1956 we have shared results and information on the project with the United Kingdom as a means of more rapidly reaching the goal we both seek.

"Periodically it occurs that first one laboratory and then another will make a useful and illuminating advance. These advances have resulted in the production and maintenance of quite high temperatures in a plasma of light nuclei and the containment of such a plasma for very brief but nevertheless appreciable lengths of time. Much longer containment, however, must be obtained and much higher temperatures reached.

"During these experiments on both sides of the Atlantic the emission of neutrons has been observed. Whether or not these neutrons are produced under thermonuclear conditions will only be ascertainable as a result of elaborate and protracted experiments.

"At a joint meeting in the United States in October, attended by scientists from both British and U.S. laboratories, information was freely exchanged. It was agreed that, although the temperatures reached in both countries suggested the achievement of neutrons from thermonuclear reactions, more work would be required to establish this as a fact.

"The realization of the production of thermonuclear neutrons, if definitely established, would be an important step—but only a step—in the long-range efforts to develop thermonuclear reactors for the production of economic power.

"Dr. Arthur E. Ruark of the U.S. Atomic Energy Commission, who heads up the several projects in the United States, has just returned from meetings at Harwell, England, on the topic and reports that the current situation is substantially the one described above.

"Three weeks ago when Sir Edwin Plowden, Chairman of the United Kingdom Atomic Energy Authority, was in the United States, we issued a joint statement to the effect that comparative observations which had been published about U.K.–U.S. progress in this field were seriously misleading. To emphasize the degree of collaboration, we arranged for substantially simultaneous publication of reports from some of the British and U.S. laboratories following the necessary concurrences on a Joint Classification Guide. The date for this publication will be as early in the new year as the papers can be made ready.

"It may be important to restate that the development of economic thermonuclear power, although I am confident that it will be realized, is still remote. It will not, therefore, interfere with the necessary development of reactors for the production of electrical energy from the fission of heavy elements."

Soviet Spokesman Describes Graduate Studies

Some aspects of graduate science education as practiced in the Soviet Union are described in a brief public report by M. Kruglyanski of the Ministry of Culture. The report, which was released in English by the Soviet Embassy in Washington, stresses the assistance that the government gives to all students who possess the interest in and ability to do scientific research. Also emphasized is the wide geographic distribution of scientific establishments in Russia. Quoted below are some of the specific points that the report makes about the various aspects of graduate science education.

Admission to graduate schools. "All citizens of the USSR, regardless of social position and origin, sex, race or nationality, have the right to enter, provided they have a higher education, at least two years of practical experience and the ability for scientific work. Only as an exception, at the recommendation of a scientific council, is one allowed to enter a graduate course immediately after graduating from college. However, even such exceptions refer only to such theoretical subjects as mathematics, physics, mechanics, astronomy, theoretical chemistry and theoretical biology."

State scholarships. "All who have qualified for entrance exams get a month's leave with pay to prepare for them. Graduate students do not have to pay for their education and all receive state scholarships. In addition they receive annual grants of one month's scholarship for the purchase of scientific literature. They are free to use equipment, laboratories, and libraries, are sent on scientific missions, participate in expeditions, etc., on the same footing as the scientific workers and teachers in the colleges and research institutes. Every year postgraduate students receive two months' paid vacation."

Academic programs. "The basic method of training is through individual work according to a definite plan under the guidance of a science instructor. Toward the end of his course, which may not exceed three years, the postgraduate student reports to the scientific council of the college or research institute on the results of his scientific work. The graduate student may submit his dissertation only if the main results of his studies have been published.

"There are also correspondence graduate courses with a four-year term, and the students enrolled in them also have a number of privileges. These include a month's leave for entrance exams, annual additional paid leave, free access to equipment and material necessary for research under the scientific program.

"There are many specialists working at higher educational and scientific research institutions, at plants and factories, and collective and state farms who are preparing their dissertations in addition to their day-to-day work. These workers get additional paid leave for finishing their theses—three months for a master's thesis and six months for a doctor's thesis."

Number and distribution of students. "Figures reveal a constant increase in the number of postgraduates. In 1939, for example, there were 12,000 postgraduate students at the colleges and scientific institutions. By 1956 this figure had risen to some 30,000. Data on the distribution of postgraduate students according to the various branches of science show the

great attention being paid to the preparation of specialists in the technical fields. These comprise approximately one-third of all postgraduate students. Second place goes to representatives of the physico-mathematical sciences and third, to the agricultural sciences."

Growth of scientific potential. "During the years of Soviet power the army of scientists has grown 24-fold and today comprises 240,000 people, more than 95,000 of whom have masters' or doctors' degrees. In 1956 alone the number of scientific workers increased by more than 15 percent. With each passing year the number of scientific establishments increases, and today there are some 3,000 of them."

Geographic distribution of establishments. "When we say that science in the USSR is developing on a broad scale, we have in mind not only the ultimate results but also the geographic distribution of scientific establishments. In Uzbekistan, for example, where before the Revolution only two percent of the population were literate, today there are 150,000 specialists with secondary technical or higher education. The republic has an Academy of Sciences and several scientific institutes which employ some 6,500 scientific workers. Before the Revolution there was practically no intelligentsia in the Kazakh Soviet Socialist Republic, whereas today there are more than 230,000 specialists with secondary technical or higher education in the republic, more than 5,000 of whom are employed by the republic's Academy of Sciences and various scientific and educational establishments."

New Standard of Length

The Advisory Committee for the Definition of the Metre, chaired by L. E. Howlett, director of the Division of Applied Physics, National Research Council of Canada, has unanimously agreed on a new standard of length—a wavelength of light—to be used instead of the platinum-iridium bar kept at Sèvres, France. The leading contenders as the source for light for the standard have been the following isotopes: mercury-198, krypton-84, krypton-86, and cadmium-114. One of the wavelengths of orange light emitted by krypton-86 has been selected as the standard, and the international meter will be defined as 1,650,763.73 times this wavelength. The resulting standard will be more than 100 times as precise as the present international meter.

Although in practice the new standard is already in use, several steps remain before the wavelength becomes officially recognized. The committee mentioned above will send its recommendation to the International Committee of Weights and Measures for consideration at its meeting in October 1958; when approved there, the recommendation will be presented to the International Conference on Weights and Measures, which will meet in 1960; at that time the standard will become the legal international standard.

Biological Science in Indonesia

The Gustavus and Louise Pfeiffer Research Foundation has recently made a grant to the department of biological sciences at the University of Indonesia in Jakarta. According to Gilbert Church, visiting chairman of the department who was sent to Indonesia as part of the University of California School of Medicine's Indonesia Project in Medical Education, the money will be used to encourage Indonesian students to continue their research in the various fields of the biological sciences, and for special equipment and supplies that may be needed but are not available in Indonesia. The research program in progress at the University of Indonesia is of special significance because heretofore almost no zoological research has been done in Indonesia.

IGY Meteorological Data

The World Meteorological Organization has announced the availability of microcards of International Geophysical Year meteorological data. The data recorded during the 18 months of the IGY will be published on approximately 18,500 microcards that will ultimately be sold in complete sets, partial sets, or individually at a price to be determined by the number of complete sets ordered. At present the estimated price for a complete set is $5990. All orders should be placed with the World Meteorological Organization, IGY Meteorological Data Centre, 1 Avenue de la Paix, Geneva, Switzerland.

Shortage of Engineers?

Fourteen young engineers recently took a room at the Statler Hotel in New York so that they could be available for employment interviews by members of the American Society of Mechanical Engineers. The society was holding its annual meeting at the Statler and at the nearby Sheraton-McAlpin Hotel.

The men, 30 to 40 years old, were laid off a month ago when the turbomotor division of the Curtiss-Wright Corporation in Princeton, N.J., was closed for lack of work. Salaries for the 14 men had ranged from $9000 to $ 5,000 annually.

S. Barron, a chemical engineer and spokesman for the group, reported that the group had received six or eight telephone calls a day. Some callers asked for more information, some asked for résumés, and some arranged interviews. However, no one was hired. When news of the employment predicament became known, the press commented on the sharp change in trend that it seemed to indicate and suggested that perhaps the current concern over a shortage of scientists and engineers was being exaggerated.

Proton Beam Brought Outside Accelerator

The University of Chicago's Enrico Fermi Institute for Nuclear Studies has announced that it has increased the research value of its 450-Mev synchrocyclotron by bringing a proton beam outside the accelerator and into a newly constructed underground experimental room. The beam, one of the most intense in the world and the first to have been brought outside an American accelerator, will permit use of the university's machine for physical and biological research not previously possible.

A meson beam, lighter and less powerful, was extracted from the atom smasher when it was first operated in 1951, but until recently studies of proton bombardment were limited to the 9-foot-square, 2-foot-thick vacuum chamber inside the cyclotron in which the protons are accelerated. With the new external beam, targets can easily be put in position and surrounded by the necessary detecting and recording equipment.

AAAS-Campbell Award

The first AAAS-Campbell award for Vegetable Research was given at the AAAS Indianapolis meeting to S. H. Wittwer and F. G. Teubner, Michigan State University horticulturists, for their joint work on flower formation and fruiting in the tomato. The award, which consists of $1500 and a bronze medal, was established in 1957 by the Campbell Soup Company. It is given for "an outstanding single research contribution, of either fundamental or practical significance, relative to the production of vegetables, including mushrooms, for processing purposes, in the fields of horticulture, genetics, soil science, plant physiology, entomology, plant pathology, or other appropriate scientific areas."

A panel of seven judges, six representing societies affiliated with the AAAS and the seventh representing the AAAS, nominated 15 scientists for the award,

and then selected the winners from the nominations. The award is based on research on the tomato that Wittwer and Teubner have carried out during the last three years. Their findings, which have led to increases in yield, have been applied to greenhouse-grown crops in Michigan, Ohio, and Indiana.

Wittwer was born at Hurricane, Utah, in 1917. He obtained the B.S. degree at Utah State College in 1939 and his Ph.D. in horticulture at the University of Missouri in 1943. Since 1946 he has been employed at Michigan State University. Teubner was born at St. Louis, Missouri, in 1927. He received the B.S. degree from the University of Missouri, Columbia, in 1949 and continued at that institution for the M.S. and Ph.D. degrees in horticulture, receiving the latter in 1953. Since then he has been at Michigan State University.

Satellite Design

Natural scientists at the California Institute of Technology have developed a cylindrical satellite that they hope will measure cosmic ray activity, temperatures, and meteoric impacts in outer space. William M. Pickering, director of the institute's jet propulsion laboratory, reports that the first flight will be made sometime between the first of the year and the end of March.

The satellite, 1 foot high and about 5 inches in diameter, will be fired in a multistage Jupiter-C rocket, under development at Redstone Arsenal, Huntsville, Ala. Incorporated in the satellite will be C.I.T.'s new "microloc" communications system, which permits transmissions over very long distances with very low power.

Grants, Fellowships, and Awards

Cancer. The American Cancer Society has announced that 1959–60 clinical fellowships at the senior resident level may be applied for by institutions accredited by the Council on Medical Education and Hospitals of the American Medical Association to give training in the following specialties, with emphasis on the diagnosis and treatment of cancer: internal medicine, malignant diseases, neurological surgery, obstetrics-gynecology, orthopedic surgery, otolaryngology, pathology, public health, radiology, surgery, and urology. The annual stipend, tax exempt, is $3600. Applications must be received before 15 February by the Director of Professional Education, American Cancer Society, Inc., 521 W. 57th St., New York 19, N.Y.

Educational Testing. The Educational Testing Service is offering a visiting associateship in science to a school or college teacher for the summer of 1958. The candidate should have a strong background in at least one of the physical sciences. The stipend is $700; transportation costs will be paid. Application forms must be received before 28 February by Mrs. W. Stanley Brown, Test Development Division, Educational Testing Service, 20 Nassau St., Princeton, N.J.

Mendeliana

The University of Illinois has acquired what are probably the only remaining letters, photographs, experiment notes, and personal papers of Gregor Mendel, founder of the science of genetics. The material was purchased from the widow of Hugo Iltis, biographer of Mendel, who assembled an extensive collection of Mendeliana at Brunn, Czechoslovakia, before fleeing the Nazis in 1939. The Mendeliana left behind in Czechoslovakia appear to have been lost or destroyed.

Mendel, a monk, published his laws of inheritance in 1865. Ignored and misunderstood, his epochal work was forgotten until his principles were rediscovered and acclaimed in 1900, and by then most of his scientific records had been discarded.

New Maser

A new amplifier that may extend the range of radio telescopes ten times farther out among the galaxies has been developed in the Gordon McKay Laboratory of Applied Science at Harvard University. This device, which may enable man to "hear" the radiation from hydrogen clouds in galaxies beyond the range of any present instruments, was operated in a laboratory test for the first time on 7 December. Scientists believe that the device will allow detection of signals 1/1000 as strong as those which can be observed now. The three-level solid state maser (the term *maser* was coined from the words *microwave amplification by stimulated emission of radiation*) was developed by Nicholaas Bloembergen, Gordon McKay professor of applied physics, who proposed the device in July 1956; J. O. Artman, research fellow in applied physics; and Sidney Shapiro, graduate student.

Thomas Gold, Harvard astronomer, reports that the Harvard College Observatory hopes soon to apply the maser to the radio telescope, with the assistance of the division of engineering and applied physics. The job cannot be done immediately because of the complicated and experimental nature of the device.

Census of Future Scientists

The U.S. Office of Education is conducting the first nationwide census of college juniors majoring in the sciences and mathematics. About 1100 colleges and universities have been invited to participate in the survey; more than 600 of these institutions have assisted in pretesting the questionnaire that is being used.

The count will provide a basis for estimating the number of new scientists and mathematicians with bachelor degrees who will be available 2 years hence, and of those with doctorates 6 years hence. Several months will be required for completion of the survey, which is to be conducted annually.

Science League

The Science League, a nonprofit association for amateur scientists who are also radio amateurs, has been founded by Nelson M. Griggs, R.D. 2, Old Baltimore Rd., Boyds, Md., for the purpose of organizing better communications channels between amateur scientists. Participants meet each evening on 3525 kilocycles at 6 P.M. E.S.T. and on 7125 kilocycles at 9 P.M. They relay information of a scientific nature to the various member clubs and individuals, and, in addition, act as a clearing house for such information as originates with them.

The Science League net in no way interferes with existing "ham" radio projects and radio nets that concern themselves with special projects. Founding members envision that the Science League will continue long after the International Geophysical Year is over. Membership is open to all.

News Briefs

The American Institute of Chemical Engineers will begin its golden jubilee year on 29 January 1958 with a commemoration of the first meeting. A golden jubilee celebration will be held 22–27 June. Both events will take place in Philadelphia, the birthplace of the institute.

* * *

A committee has been formed to establish, in honor of Samuel Brody, a lectureship memorial in agricultural science at the University of Missouri. Contributions may be mailed to the Samuel Brody Memorial Committee, Eckles Hall, University of Missouri, Columbia.

* * *

A Committee of the Section of Biochemistry, International Union of Biological Sciences, has recently been formed. It is essentially a coordinating

committee between the IUBS and the International Union of Biochemistry. The committee is specifically concerned with chemical biology within the framework of the unions federated in the International Council of Scientific Unions. An important function of the committee will be to make proposals for international symposia to both IUBS and IUB. It is hoped that a full committee meeting will shortly be held, perhaps during the 4th International Congress of Biochemistry in Vienna in September 1958.

The committee, as at present constituted, consists of M. Florkin (Liége), president; O. Lindberg (Stockholm); R. Brunel (Toulouse); F. Lynen (Munich); P. Boyer (Minneapolis); and T. W. Goodwin (Department of Biochemistry, University of Liverpool), secretary.

* * *

A colony of 12,000 mice, representing 20 to 30 inbred pure genetic strains, will be maintained at the University of Michigan Laboratory of Mouse Genetics when renovations for converting the Laboratory of Vertebrate Biology are completed. A grant of $111,843 from the National Institutes of Health, U.S. Public Health Service, has supported the renovation. Five similar centers will be set up throughout the country with NIH support.

* * *

Southern Methodist University has opened a computing laboratory. A new building houses a Univac scientific 1103 computer, the Remington Rand Service Bureau, and the S.M.U. Computing Laboratory offices and classrooms. The computer is operated jointly by Remington Rand as a service to industry and by S.M.U. as an academic service for research and teaching. The S.M.U. operation is associated with the university's new Graduate Research Center. Professors and students may use the machine for academic research and training. Computing projects are now under way in the fields of engineering, mathematics, psychology, law, religion, management and others.

Scientists in the News

RAYMOND M. G. BOUCHER, former head of the Aerosols Department, Experimental Laboratory, National Conservatory of Arts and Sciences in France, has been appointed head of a new research program in airborne ultrasonics at the Vibro-Ceramics Division of Gulton Industries, Inc., Metuchen, N.J.

VLADIMIR HAENSEL, director of refining research, Universal Oil Products Company, Des Plaines, Ill., has received the Professional Progress Award of the American Institute of Chemical Engineers for his "important contributions to the development of catalytic processes for the treatment of petroleum products."

Also, THOMAS J. HANRATTY, assistant professor of chemical engineering at the University of Illinois, has received the A.I.Ch.E. Junior Award for excellent contributions to A.I.Ch.E. publications by a younger member of the Institute.

BRUNO OETTEKING has retired from Columbia University and from the Museum of the American Indian, Heye Foundation, New York. Also, he has been named a corresponding member of the German Anthropological Association.

ANTONI K. OPPENHEIM, associate professor of mechanical engineering at the University of California, Berkeley, has been appointed visiting professor of engineering in the department of chemical and metallurgical engineering at the University of Michigan.

R. G. ORELLANA, after completing an assignment in Peradeniya, Ceylon, for the Food and Agricultural Organization's Technical Assistance Program, has resigned his position with the Inter-American Institute of Agricultural Sciences in Costa Rica. He has been appointed plant pathologist in the Oilseed and Industrial Crops Research Branch of the U.S. Department of Agriculture in the division of plant pathology, University of Florida, Gainesville. He is now investigating diseases of castorbean and sesame.

PAUL A. SIPLE, antarctic explorer, has received the Army's Distinguished Civilian Service Award for his scientific leadership at the South Pole. Siple has just returned from Antarctica, where he has been serving since October 1956 as deputy to the officer in charge of the United States antarctic programs for the International Geophysical Year.

C. E. DAVIS has retired as secretary of the American Society of Mechanical Engineers after 23 years of service in that office and nearly 38 years in the service of the society. Davis will continue to serve as coordinator for the United Engineering Center. He is succeeded in the secretaryship by O. B. SCHIER, II.

The last three in the series of five William Pyle Philips Lectures on advances in microbiology will take place at Haverford College as follows: 13 Feb., DAVID M. BONNER of Yale University, "Genes and Their Action"; 12 March, JOSHUA LEDERBURG of the University of Wisconsin, "Reproductive Versatility in Bacteria"; and 11 Apr., ARTHUR KORNBERG of Washington University, "Enzymatic Approaches to the Chemical Basis of Heredity." The two first lectures were delivered by S. E. LURIA of the University of Illinois and ROGER Y. STANIER of the University of California.

HOWARD P. McCOLLUM has recently been appointed supervisor of science for the state of Louisiana. Similar appointments affecting science teaching have been made in North Carolina, Connecticut, New York, Pennsylvania, and New Mexico.

PAUL E. BROWN, formerly a senior engineer with the General Electric Company, has accepted a position with Argonne National Laboratory as an associate engineer in the reactor engineering division.

CLARK T. ROGERSON, assistant professor of botany at Kansas State College and assistant mycologist at the Kansas Agricultural Experiment Station, has been named curator of the cryptogamic herbarium of the New York Botanical Garden, effective 1 February. Dr. Rogerson's special studies have been on the parasitic fungi of Kansas and the taxonomy of Ascomycetes and the Hypocreales.

Recent Deaths

F. A. BANKS, San Marino, Calif.; 74; U.S. Reclamation Bureau engineer, became responsible in 1933 for the construction of Grand Coulee Dam; supervised the dam's operation until 1950; 14 December.

C. F. BECKWITH, New York; 70; mechanical engineer and cofounder of Aqua Systems, Inc., manufacturers of equipment for gasoline service stations; 17 December.

HENRY C. CORTES, Dallas, Tex.; 65; vice-president and director of Magnolia Petroleum Company; 6 December.

H. ELIASBERG, New York; 67; associate clinical professor of pediatrics at Cornell University Medical College; co-discoverer in 1920 of epituberculosis; 16 December.

GUSTAF W. ELMEN, Englewood, N.J.; 80; former metallurgist at Bell Telephone Laboratories and specialist in magnetic research; 10 December.

EARL T. ENGLE, Suffern, N.Y.; 61; professor of anatomy at the College of Physicians and Surgeons of Columbia University; 17 December.

HARVEY A. K. WHITNEY, Ann Arbor, Mich.; 63; founder of the American Society of Hospital Pharmacists; 15 December.

Erratum: On page 1173 of the 6 December issue of Science, it was stated incorrectly that Floyd H. Allport is professor emeritus at the University of Oregon. He is professor emeritus at Syracuse University.

Reports

Segregation Analysis in Human Genetics

Thirty years ago, the infant science of human genetics was largely concerned with accumulating examples of regular Mendelian inheritance. By the methods of that period, devised by Weinberg, Bernstein, and others, it was not difficult to recognize traits that approximated monogenic inheritance, at least in some pedigrees. However, as larger and more representative samples were collected, many of these conditions appeared to deviate from simple Mendelian models in ways that suggested sporadic cases of mutational or nongenetic origin, mixture of genetic entities, differential viability, incomplete penetrance, or irregularities in the sampling ("ascertainment") procedure. Human geneticists have become increasingly interested in these discrepancies as critical evidence on the inheritance, gene frequencies, mutation rates, genetic risks, selection pressures, and homogeneity of genetic traits.

As soon as deviations from the simplest models were encountered, the traditional statistical methods of human genetics became inadequate. In some cases these methods have been found to be unreliable in small samples (*1*). More generally, they fail to provide tests of internal consistency or to distinguish among alternative hypotheses which in principle are quite distinct, such as partial sex-linkage and sex-biased manifestation, or mutations, phenocopies, and incomplete penetrance. Further progress in many aspects of human genetics must await the application, not only of better laboratory techniques, but also of a more refined methodology, made possible by modern developments in mathematical statistics.

Segregation and recombination, the basic data of formal genetics, pose contrasting analytical problems. (Segregation relates to the distribution of progeny with respect to a single genetic locus, and recombination, to the element introduced when two loci are considered simultaneously.) The alternative to 50 percent recombination is linkage with some smaller recombination value, whose a priori distribution is in principle specifiable and can in fact be approximated. Usually no other parameter need be estimated, nor the ascertainment of the main locus specified. Here is a problem differing from that usually encountered in scientific research in being amenable to the acceptance sampling theory of Neyman and Wald, which assumes a formal alternative to the null hypothesis. These small-sample methods, adapted to sequential analysis, are of all linkage tests in man the most precise, powerful, and utilitarian (*1, 2*).

Segregation, on the other hand, opposes a variety of alternatives to the null hypothesis that specifies the proportion affected p (for example, $p = 1/8$ for an intercross with 50-percent penetrance of the recessive homozygote). The true proportion may be larger or smaller than this, the ascertainment model may be incorrect, or segregation may be confused with sporadic cases of different etiology, and to these alternatives no a priori probabilities can reasonably be assigned. To such problems, characteristic of scientific research, acceptance sampling theory provides no solution. Fortunately, human families give much more information about segregation than about recombination, so that large-sample theory is appropriate. The maximum likelihood theory of Fisher is the method of choice, since to its excellent theoretical credentials may be added the advantage of analysis by simple addition of iterative scores. This application was initiated by Finney (*3*) and has now been extended to a number of common genetic situations. It is the purpose of the present report (*4*) to indicate the logical structure of this extension so that practitioners of human genetics may choose methods of analysis appropriate to their data. A full exposition, with derivation of formulae and tables of scores, is in preparation.

The expected proportion affected p (assumed constant among families of a particular mating type) is specified by Mendelian theory if penetrance is complete. With incomplete penetrance, a simple analysis must be restricted to matings with the same theoretical proportion, which is multiplied by the penetrance to obtain the effective proportion p. For example, if onset is delayed, the penetrance will lie between

$$\int f(z)\,G(z)\,dz$$

and

$$\int f_1(z)\,G(z)\,dz$$

where $f(z)$ is the frequency of age z at death or last examination among affected individuals and their normal sibs, $f_1(z)$ is this frequency with the first proband in each family excluded, and $G(z)$ is the cumulative frequency of onset at age z among affected cases. Any treatment of incomplete penetrance must be approximate if there is interfamily heterogeneity in penetrance or age of onset, but maximum likelihood scores provide empirical standard errors against which genetic hypotheses may be tested.

Incomplete ascertainment is one of the most troublesome problems in human genetics and requires a special vocabulary. A proband is an affected person ascertained independently of the other affected members of the family. The ascertainment probability π (assumed to be independent of the number of affected sibs, the severity of their affection, and the number of probands among sibs) is the probability that an affected person be a proband. The ascertainment probability approaches zero if very few affected family members are probands (*single selection*) and unity if there is complete selection of affected children (*truncate selection*). In the general case of multiple selection ($0 < \pi \leq 1$), there will be a probands in a sibship with r affected, with probability

$$P_{(a)} = \frac{\binom{r}{a}\pi^a(1-\pi)^{r-a}}{1-(1-\pi)^r}$$

where $1 \leq a \leq r$. Each proband may be independently ascertained t times

$$P_{(t)} = \frac{(1-\pi)[-\ln(1-\pi)]^t}{t!\pi}$$

with $t \geq 1$. Comparison of scores for π from $P_{(a)}$ and $P_{(t)}$ provides a test of the hypothesis that sources of ascertainment are independent. This granted, the scores may be pooled for comparison with a third sum of scores, obtained from the distribution of r among families. The more information about π that can be derived in these ways, the more precise the tests on other parameters will be. Information from the distribution of t has apparently never before been used.

At this point it is necessary, for clar-

All technical papers and comments on them are published in this section. Manuscripts should be typed double-spaced and be submitted in duplicate. In length, they should be limited to the equivalent of 1200 words; this includes the space occupied by illustrative or tabular material, references and notes, and the author(s)' name(s) and affiliation(s). Illustrative material should be limited to one table or one figure. All explanatory notes, including acknowledgments and authorization for publication, and literature references are to be numbered consecutively, keyed into the text proper, and placed at the end of the article under the heading "References and Notes." For fuller details see "Suggestions to Contributors" in *Science* 125, 16 (4 Jan. 1957).

ity, to distinguish between *isolated* and *sporadic* cases. Isolated cases may be of the same origin as familial cases, and the absence of affected sibs due to chance, or they may be sporadic, of different origin (mutation, phenocopy, and so forth). To distinguish between incomplete penetrance and sporadic cases, we may recognize a quantity x, the frequency of sporadic cases among affected cases in the population, and test the hypothesis that no isolated case is sporadic ($x = 0$). For example, if a trait is sometimes due to a rare dominant gene, the probability that an affected parent with s children have at least one affected child is

$$P_{(r>0)} = (1-x)(1-q^s)$$

where $q = 1 - p$, and the scores for x give a specific, and the most efficient, test for the existence of sporadic cases not transmissible to the progeny.

If families are ascertained through parents or other relatives without regard to the children, and if $x = 0$, the probability of a segregating family ($r > 0$) is

$$P_{(r>0)} = (1-h)(1-q^s)$$

for possible backcrosses, and

$$P_{(r>0)} = (1-h)^2(1-q^s)$$

for possible intercrosses, where h, the probability that a parent of dominant phenotype be homozygous, is determined under random mating by the gene frequencies. Using this theoretical value of h, we may compare the scores for p from segregating and nonsegregating families with the scores from the distribution of r in segregating families as a test of the hypotheses that $x = 0$ and that mating is at random with the specified gene frequencies.

If $x\mu \ll (1-x)p$, where μ is the proportion affected among sibs of sporadic cases, then familial cases of sporadic origin may be neglected, and the probabilities for isolated and familial cases, respectively, are

$$P_{(r=1|r>0)} = \frac{sp\pi[(x+(1-x)q^{s-1}]}{xsp\pi + (1-x)[1-(1-p\pi)^s]}$$

and

$$P_{(r|r>1)} = \frac{\binom{s}{r} p^r q^{s-r}[1-(1-\pi)^r]}{1-(1-p\pi)^s - \pi sp q^{s-1}}$$

The distribution of r for familial cases gives a third sum of scores for π and a test of the null hypothesis about p, independent of x, while the distribution of isolated and familial cases tests the hypothesis that $x = 0$, or permits an estimate if this hypothesis is rejected.

Sex-linked genes present interesting problems, such as that of distinguishing the mutation rates in the two sexes. However, for a decisive analysis, more penetrating methods are required than have so far been applied to this question. For a deleterious sex-linked recessive trait, the probability that an affected male be sporadic is

$$x = mu/(2u+v)$$

where m is the coefficient of selection against affected males, u and v are the mutation rates in egg and sperm, respectively, and it is assumed that carrier females have normal fertility and that all cases are sex-linked. The test of the hypothesis that $u = v$ reduces to testing whether $x = m/3$.

Corroboration of this test may be sought in the distribution of affected maternal uncles, assuming ascertainment through nephews. If two or more nephews are affected, the probability that at least one of s maternal uncles be affected is

$$P_{(r>0)} = (1-x')(1-q^s)$$

where the expected value of x' is ½ on the hypothesis of sex linkage. Similarly, if only one nephew is affected in a sibship of n nephews, the probability that at least one maternal uncle be affected, if ascertainment is through the nephew, is

$$P_{(r>0)} = \frac{(1-x)(1-x')q^{n-1}(1-q^s)}{x+(1-x)q^{n-1}}$$

These distributions provide a test of homogeneity of x and of x', of the deviation of x' from ½, and of x from $m/3$, the last deviation being accepted as significant only if the others are nonsignificant.

These ancillary tests are particularly important if sex-linked and autosomal cases may be confused, in which event families with autosomal or sporadic cases may be recognized if they contain at least one affected girl. The probabilities for isolated and familial cases under this condition are given in Fig. 1.

Genetic tests in man have never been carried out with the precision of these methods, the practical limitations of which cannot therefore be specified. Considerable caution should be exercised in analysis of medical literature or other biased sources, or if correct diagnosis is more likely in familial cases. However, it is still possible that the distribution of r for familial cases may be adequately described by the formulae of this report.

With careful enumeration of probands and ascertainments when π is less than 1, these methods should be sufficiently general for almost any Mendelian analysis, provided that the mating types to be analyzed do not contain a mixture of segregation frequencies. (Common genes with low penetrance will continue to defy precise analysis.) For the typical case of a rare or highly penetrant gene, the method of maximum likelihood scores for p, x, h, and π, applied to the distributions of this report, will provide a simple and more powerful analysis than has been previously available.

$$P_{(r=1|r>0)} = \frac{sp\pi[x+(1-x)q^{s-1}]}{xsp\pi + 2(1-x)[1-(1-p\pi)^s - (\frac{1}{2}p+q)^s + (\frac{1}{2}p+q-\frac{1}{2}p\pi)^s]}$$

$$P_{(r|r>1)} = \frac{\binom{s}{r} p^r q^{s-r}[1-(1-\pi)^r][1-(\frac{1}{2})^r]}{1-(1-p\pi)^s - (\frac{1}{2}p+q)^s + (\frac{1}{2}p+q-\frac{1}{2}p\pi)^s - (\pi sp q^{s-1})/2}$$

Fig. 1. Probabilities for different numbers of affected children under multiple selection with at least one affected girl.

NEWTON E. MORTON
Department of Medical Genetics, University of Wisconsin, Madison

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31 July 1957

Structure of Adenine Polynucleotide

The x-ray diffraction pattern of untreated individual fibers of enzymatically synthesized adenine polynucleotide has been presented and discussed by Watson (*1*). A more crystalline preparation of the polymer has been obtained from material synthesized by Roland F. Beers, Jr., (*2*), spun into a bundle of fine fibers, and stretched while bathed in a heated mixture of ethanol and dichloroacetic acid (DCA) (*3*). The distribution of intensity on the x-ray diagram of these fibers is similar to that given by untreated fibers, showing that the form of the molecule is not greatly altered; differences of detail are observed, however, chiefly on the equator and on the first layer line. The 13 reflections here observed indicate a tetragonal unit cell, 22.6 by 22.6 by 15.0 A. A fourfold screw axis is evident parallel to the fiber axis, with translation of 3.75 A. The observed density of these fiber bundles (~1.60) suggests 16 nucleotide residues and 16 molecules of DCA per unit cell (calculated density, 1.66).

Ochoa and Heppel (*4*) have demonstrated that adenine polynucleotide is a 3′5′ adenosine diester of phosphoric acid. Furberg (*5*) has given bond distances and angles appropriate for a β-D-riboside; Broomhead (*6*) and Cochran (*7*) for adenine; Dunitz and Rollett (*8*) for a phosphoric acid diester. Barton and Cookson (*9*) and Mizushima (*10*) have summarized the principles of "conformational analysis." Using the above information and assuming that the polymer has no branches, we have deduced the probable preferred orientations of the groups around each of the six single bonds in the main chain of the polymer. The method developed by Bear (*11*) for collagen was then employed to exhibit, in a systematic way, all possible configurations of such a chain which would fit the several helix-net interpretations of the fourfold screw. The configurations fell into six main groups, in each of which one or more ways of satisfying net requirements were found. However, only three models capable of containing the required number of chains with atoms confined to radial limits of about 8 A could be built. One of these was discarded because the adenine–ribose bond was parallel to the fiber axis, which is expected to result in positive double refraction in contradiction to the negative sign observed by Rich (*12*). The remaining two, termed structures I and II, both have the planar adenine moieties perpendicular to the fiber axis, and both are adaptable to the observed unit cell as chain pairs whose pair axes run through the corners and the center of the square basal cell section.

The space group of structure I is $P4_322$. The fourfold screw is left-handed, and the two chains of each pair are related to each other by the perpendicular dyad axis. They are held together by a pair of reciprocal OH—O bonds of length 2.84 A between the O′-2 of one ribose group and the O′-1 of the other in each residue pair. The bonding is similar in type and length to that between O-1 and O-5 in glucose as determined by McDonald and Beevers (*13*). The P=O's of one chain are in contact with those of the other in the next turn of the screw. The adenine groups of any one double helix are in van der Waals contact in sets of two, and between any two adjacent double helices the bases form a solid column because of interpenetration.

The two chains of structure II are related by a dyad parallel to the fiber axis and are held together by a reciprocal pair of NH—N bonds between N-10 and N-1 of the adenine groups (pairing No. 2 of Donohue, *14*). The systematic analysis of stable chain conformations led to this pairing rather than to pairing No. 1 of Donohue, which has been employed by Watson (*1*) in an otherwise quite similar model. No other intramolecular H-bonds are here possible. The screw is now right-handed, and the space group is $P4_2$. Preliminary coordinates for both models are given in Table 1.

Fig. 1 shows, with vertical bars, the position in reciprocal space (and an indication of the relative intensity) of the reflections given by DCA-treated fiber bundles of adenine polynucleotide. Under each reflection is its index in the tetragonal lattice. On the right half of the figure in curving lines is the position of intensity shown on optical transforms (see Wyckoff *et al., 15*) of a single double helix of type I in projection perpendicular to the dyad axis (solid line) and in projection 45° to the dyad (dotted line). On the left is shown the location of intensity due to similar transforms of structure II in projection perpendicular to the x-axis (solid line) and 22½° to this axis (dotted lines). The intensities shown on each equator were derived from projections perpendicular to the fiber axis. Except for the equator for structure I, the optical transforms included neither cation nor DCA. The equatorial intensities for structure I include 16 DCA molecules placed in the cell to bind adjacent double helices. The transform of structure II lacks intensity in the (401)-(421) region of reciprocal space. With structure I, the regular oc-

Table 1. Right-handed Cartesian coordinates for structures I and II in angstroms.

Atom	Structure I			Structure II		
	x	*y*	*z*	*x*	*y*	*z*
C′-1	4.33	2.34	0.00	6.45	2.15	0.00
C′-2	4.37	1.67	1.32	7.50	2.00	−1.03
C′-3	3.03	2.05	1.83	6.80	2.90	−2.11
C′-4	2.08	2.00	0.65	6.25	4.05	−1.33
C′-5	0.95	2.90	1.10	4.90	4.80	−1.74
O′-1	3.03	1.87	−0.50	5.85	3.40	0.00
O′-2	4.62	0.30	1.40	8.85	2.10	−0.69
O′-3	2.36	1.36	2.88	7.75	3.20	−3.10
O′-5	2.20	0.35	5.00	4.50	5.85	−0.80
P	3.17	1.30	4.20	3.25	6.75	−0.60
OH	4.67	1.45	4.55	4.10	7.90	−0.90
=O	2.30	2.45	4.40	2.05	5.90	−0.60
N-1	3.55	7.40	0.00	1.50	1.10	0.00
C-2	2.65	6.35	0.00	2.10	2.30	0.00
N-3	2.95	5.10	0.00	3.45	2.45	0.00
C-4	4.30	4.90	0.00	4.10	1.25	0.00
C-5	5.30	5.85	0.00	3.55	0.00	0.00
C-6	4.90	7.20	0.00	2.15	−0.15	0.00
N-7	6.55	5.25	0.00	4.55	−0.95	0.00
C-8	6.25	3.95	0.00	5.65	−0.20	0.00
N-9	4.95	3.67	0.00	5.45	1.10	0.00
N-10	5.70	8.20	0.00	1.50	−1.25	0.00

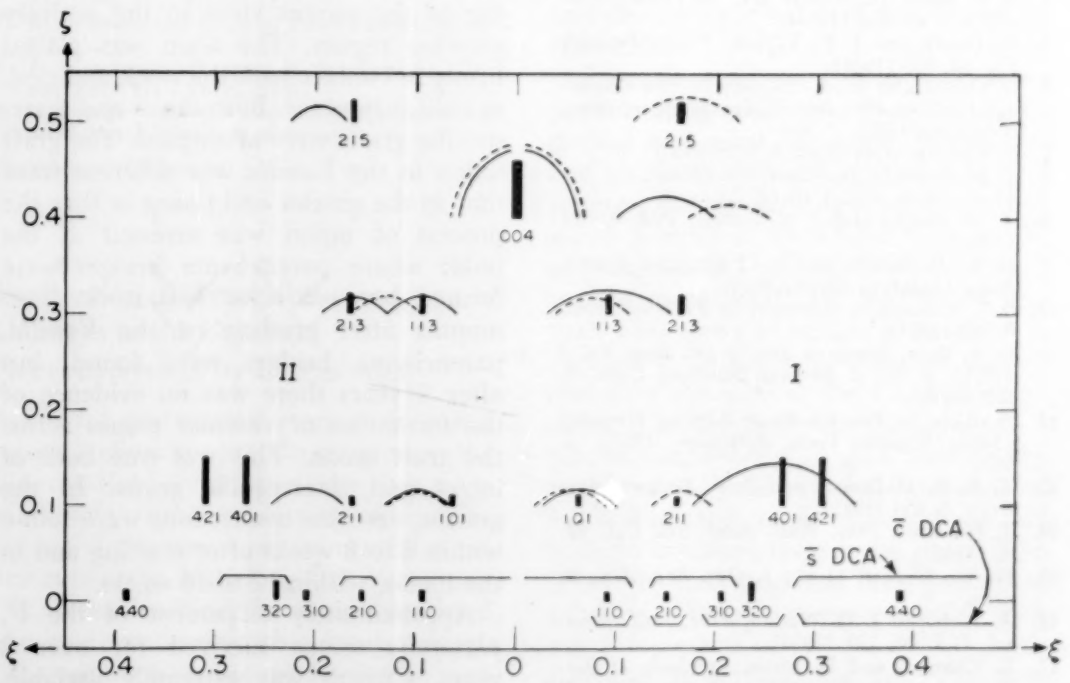

Fig. 1. Comparison of diffraction intensities.

currence of nearly planar H-bonded furanose rings, separated by approximately 5 A and tilted 20° to the fiber axis, is responsible for the great intensity seen in this area. It is these reflections, in fact, which constitute the most striking similarity between the diagrams of adenine polynucleotide and ribonucleic acid (RNA) and their greatest contrast to that of deoxyribonucleic acid (DNA).

Because the x-ray diffraction pattern of adenine polynucleotide resembles that of RNA (*16*) (and differs from that of DNA), it is expected that the structures of adenine polynucleotide and RNA are similar. The form of H-bonded backbone described for structure I above can serve as a basis for the structure of RNA, since any sequence of purines or pyrimidines can be accommodated on either chain and the configuration depends, for its regularity and stability, only on that feature of the chain which distinguishes RNA (and the synthetic polyribonucleotides) from DNA—namely, the hydroxyl group on C′-2 of the sugar moiety. Furthermore, the 6-keto and 6-amino groups of both purines and both pyrimidines would, in this kind of structure, fall at almost exactly equivalent positions. This offers the possibility of their bonding to amino acids or other molecules in a structurally regular way despite their seeming disparity of size. Chargaff and Elson (*17*), who have demonstrated the numerical equality of these groups, have also suggested such a type of bonding (*18*).

RICHARD S. MORGAN*
RICHARD S. BEAR†
Department of Biology, Massachusetts Institute of Technology, Cambridge

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* Present address. Children's Cancer Research Foundation, Boston, Mass.
† Present address: Division of Science, Iowa State College, Ames.

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Role of Parenchyma Cells in Graft Union in Vanilla Orchid

The successful grafting of numerous monocotyledons has been previously reported (*1, 2*). This work demonstrated that grafts could be made in several grass species and in certain monocotyledonous tropical lianas. It was shown that, contrary to accepted usage, a cambium was not essential for graft union but that any meristematic tissue was suitable for this purpose. The principle that any meristematic tissue is capable of forming a union between scion and stock was extended to another monocotyledonous group, the Orchidales, in the study described in this report.

The vanilla orchid of commerce, *Vanilla planifolia* Andr., is susceptible to a root rot, *Fusarium* sp., which has nearly destroyed the industry in Puerto Rico. Attempts were made, therefore, to graft *Vanilla planifolia* on another species, *V. phaeantha* Reichenb., which is resistant to the fungus. The method used was similar to that previously described for grafting lianas (*2*). Like the lianas, *Vanilla* has no definite intercalary meristem, but the actively growing tips remain meristematic. The stem of the *V. phaeantha* stock was broken in the third to fifth internode. A paper tube dipped in paraffin was slipped over the stock, and a scion of *V. planifolia* of equal diameter was inserted into the tube. The scion, also, had been obtained by breaking of the parent stem in the actively growing region. The scion was placed firmly in contact with the stock and tied, to hold it in place. Both intra- and interspecific grafts were attempted. The graft union in the *Vanilla* was different from that in the grasses and lianas in that the process of union was arrested at the point where parenchyma bridges were formed between scion and stock. Two months after grafting of the *Vanilla*, parenchyma bridges were found, but after 2 years there was no evidence of the formation of vascular tissues across the graft union. This was true both of intra- and interspecific grafts. In the grasses, vascular connections were found within 6 to 8 weeks after grafting and in the lianas, within 12 to 16 weeks.

Approximately 5 percent of the *V. planifolia* scions survived for over 2 years. Growth was extremely variable. Some scions began growth within 2 months and grew to a length of several feet, whereas others lived for a year or more before growing. During this time they retained their original leaves. Growth was slow in the majority of cases. If the nodal roots which hold the plant to its support were permitted to grow into the soil, the stock died, and the scion then persisted on its own roots.

Tests were made in which the bases of scions were dipped in coconut milk, in coconut milk plus one part per million of 2,4-D, and in one part per million of 2,4-D in water solution. Coconut milk appeared to have a beneficial effect, and it was possible to pick out the scions dipped in coconut milk by their better color and vigor. Dipping in coconut milk plus 2,4-D, or in 2,4-D water solution, was deleterious.

Wardlaw (*3*) found that if the shoot apex of certain ferns was isolated from the surrounding leaf primordia and stelar tissue by vertical cuts, it continued to grow and produce both vascular tissue and leaf primordia. No connection took place between the newly formed vascular tissue and that formed prior to the surgery, and all translocation was across parenchyma cells. The experiments reported in the present paper demonstrate that *Vanilla* grafts can survive and grow for at least 2 years on parenchyma unions. These parenchyma cells must, therefore, serve for both upward and downward translocation, since they form the only union between scion and stock. These results suggest the possibility that parenchyma cells could play a similar role in intact plants.

THOMAS J. MUZIK*
Federal Experiment Station, Mayaguez, Puerto Rico

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* Present address: Department of Agronomy, State College of Washington, Pullman.

12 August 1957

Amino Acid Factor in Control of Abscission

The role of indoleacetic acid in the control of abscission of plant organs has been demonstrated repeatedly since Laibach (*1*), in 1933, first observed that orchid pollinia retarded the abscission of debladed petioles. Addicott and Lynch (*2*) have reviewed other factors which may affect abscission, including acidity, ethylene, mineral metabolites, carbohydrate level, auxin gradients, oxygen, and carbon dioxide. Several of these have been shown to exert indirect effects in the control of abscission. The effect of

Table 1. Effects of amino acids upon the time required for abscission of unfertilized ovaries of two varieties of tobacco. The figures show average time in hours from anthesis to completion of abscission.

Lizard's Tail		Little Turkish	
0.01*M*	0.1*M*	0.01*M*	0.1*M*
	Methionine		
24	20	31	26
	Leucine		
50	38	80	40
	Alanine		
57	45	85	60
	Glutamic acid		
57	45	112	60
	Valine		
80	50	130	90
	Cystine		
98	89	170	161
	Cysteine		
94	No abscission	126	No abscission
	Control (water)		
99	93	176	165

others is uncertain at present, but it is generally agreed that indoleacetic acid plays a major role in the control.

The dissolution of the middle lamella of the cell wall during abscission was described first by Lee (*3*). Facey (*4*), through microchemical tests, characterized the dissolution as a change of calcium pectate into pectic acid which, in turn, is changed to water-soluble pectin. Recently Cormack (*5*) has emphasized the calcium pectate character of the cementing layer between cells. Ordin, Cleland, and Bonner (*6*) have reported that the methyl carbon atom of labeled methionine is rapidly incorporated into the pectic materials of cell walls of *Avena* coleoptile sections, and Byerrum and Sato (*7*) have also reported the incorporation of the methyl group of methionine in pectin isolated from radish plants. These observations suggest that methylation of the carboxyl groups of adjacent pectin molecules may be involved in the splitting of calcium bridges leading to abscission and that the amino acid methionine may serve as a methyl group donor. Experimental evidence indicates that an amino acid factor does, in part, control abscission.

Two varieties of *Nicotiana tabacum*, namely Lizard's Tail and Little Turkish, were grown under uniform greenhouse conditions and used as experimental plants. Various aqueous solutions of L-amino acids (DL-methionine, DL-leucine, DL-valine), after being adjusted to *p*H 6.0, were injected directly into the unfertilized ovaries of flowers at the time of anthesis by means of glass tubing drawn to a fine point. In 24 hours, 0.15 to 0.2 ml of the solution were taken up by the tissue. Fertilization was prevented by covering the stigma with a small foil cylinder. The results of such treatment upon the abscission of the flowers are tabulated in Table 1, for a representative experiment. Each value represents the average time required for abscission to occur for ten flowers on one plant. Cysteine at a concentration of 0.1*M* proved toxic, as evidenced by a shriveling of the tissue without the occurrence of abscission.

The effect of methionine is quite remarkable, the time for abscission of the ovary on Lizard's Tail plants being reduced from 4 days to 1 day, and the time for abscission of the ovary on Little Turkish plants being reduced from 7 days to 1 day. A significant acceleration of abscission was also obtained with leucine, alanine, and glutamic acid. Although the role of methionine as a methyl donor in organisms is well established (*8*), there is little or no information on the general aspects of methylation or transmethylating systems. The effects of amino acids other than methionine may result from their serving as methyl donors directly or from transformations giving rise to labile methyl radicals.

These observations suggest that methionine, as a methyl donor, and indoleacetic acid interact to control abscission (*9*).

ROBERT E. YAGER
ROBERT M. MUIR

Department of Botany,
State University of Iowa, Iowa City

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28 October 1957

Production of Reversible Changes in the Central Nervous System by Ultrasound

For the past several years an intensive research effort has been in progress at the Bioacoustics Laboratory of the University of Illinois on the production of selective lesions in the tissues of the central nervous system by high intensity ultrasound (*1*). Considerable information has been obtained concerning the dosage conditions required for the production of such lesions, and neuroanatomical studies utilizing this technique are now in progress. Relatively recent electrophysiological investigations indicate that *reversible* suppression of transmission along neural pathways can be accomplished by applying a controlled dosage of ultrasonic radiation at various sites along these pathways (*2*). By irradiating with ultrasound in the lateral geniculate nucleus it is possible to suppress temporarily the potential usually evoked in the visual cortex in response to a light stimulus. It should be noted that this effect is produced by a dosage of ultrasound which does not cause any histologically observable lesion in the tissue. This ultrasonic technique of producing reversible changes offers unique opportunities for three-dimensional mapping of central nervous system function.

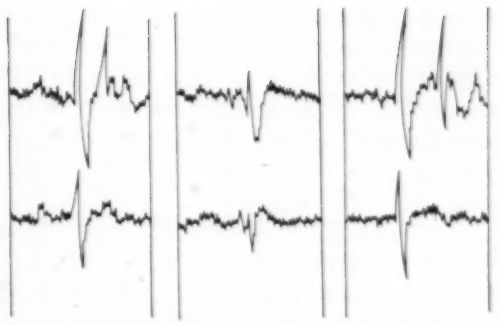

Fig. 1. Cortical potentials evoked by a flash of light (left) before irradiation, (middle) at the termination of irradiation, (right) 30 minutes after irradiation.

Bipolar recording electrodes are placed in the appropriate cortical areas on both hemispheres to detect the evoked potentials. The focused ultrasonic beam source is used to irradiate the region of one of the lateral geniculate nuclei of the animal (cat) since these nuclei are sites of synaptic stations along the visual pathway. The ultrasonic energy must be transmitted from the irradiator to the brain through degassed Ringer's solution, and the intervening skull bone must be removed.

Stimulation of the eye by light is repeated at fixed time intervals before, during, and after ultrasonic irradiation, and continuous electrical recording is in progress during the course of the experiment. A series of three light flashes, with approximately 3 seconds between flashes, is used to stimulate the eye of the animal. This series of flashes is repeated at variable intervals of time before, during, and after exposure to the ultrasonic radiation. The focus of the sound beam is placed successively in and around the region of the lateral geniculate nucleus. With a suitably chosen sound level and with an exposure time in the range from 20 to 120 seconds, it has been possible to produce reversible suppressions of various components of the elicited electrical response in the visual cortex. The type of result illustrated in Fig. 1 has been ob-

tained in a number of animals. Figure 1 shows the cortical potentials (two electrodes) evoked by a flash of light (i) before ultrasonic irradiation, (ii) at the termination of the ultrasonic exposure period, and (iii) subsequent to irradiation. At the termination of the ultrasonic irradiation period the amplitude of the primary response (upper record) was reduced to less than one-third of its original value. The amplitude of the secondary response (upper record) was reduced to practically zero. Complete recovery of the primary and secondary response was apparent 30 minutes after exposure.

Experiments are in progress to quantify further the conditions for producing controlled reversibility and to determine the site or sites (synapses, axons, cell bodies) of action of the sound (*3*).

F. J. Fry

*Bioacoustics Laboratory,**
University of Illinois, Urbana

H. W. Ades

Division of Neurophysiology and Acoustics, U.S. Naval School of Medicine, Pensacola, Florida

W. J. Fry

*Bioacoustics Laboratory,**
University of Illinois

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* The name of the Bioacoustics Laboratory was recently changed to Biophysical Research Laboratory of the College of Engineering.

14 October 1957

Effects of Caffeine and Chlorpromazine on the Sexual Behavior of Male Rats

Although the effects of stimulant and tranquilizing drugs on sexual behavior are of considerable importance, the amount of systematic research on this problem has been negligible. Soulairac and Coppin-Monthillaud (*1*) have reported that after an injection of 30 mg of caffeine (and sodium benzoate) per kilogram, male albino rats decreased their latency to first sexual activity and increased their rate of copulation. The study described in this report (*2*) compares the effects of moderate doses of caffeine and chlorpromazine on the sexual performance of 17 150-day-old male hooded rats. The previous sexual behavior of the rats varied from complete impotence to extreme vigor.

Table 1. Average performance for various criteria of sexual behavior. (No. included two subjects which did not perform at all on any of the trials.)

Behavioral measures	No.	Caffeine	No drug	Chlorpromazine	Friedman analysis of variance
Latency to:					
(i) first mount	9	13.4	26.4	69.7	$\chi^2 = 10.1$*
(ii) first copulation	9	13.4	28.3	71.3	$\chi^2 = 9.5$*
(iii) ejaculation	6	436.7	589.2	528.3	$\chi^2 = 7.0$†
Frequency of:					
(i) mounts	15	4.1	4.7	3.9	Not significant
(ii) copulations	15	16.1	15.1	12.0	$\chi^2 = 7.4$†
Percentage of group that:					
(i) copulated	15	80	87	87	Not significant
(ii) ejaculated	15	47	50	47	Not significant
Copulatory rate:					
(i) for subjects that copulated	9	2.41	1.87	1.45	$\chi^2 = 8.7$*
(ii) for subjects that ejaculated	6	2.80	1.64	1.63	$\chi^2 = 9.2$*

* Significant beyond the 0.01 level of probability. † Significant beyond the 0.05 level of probability

Each male was given four 15-minute tests, spaced at least 2 days apart. Males were injected with 20 mg of caffeine (and sodium benzoate) per kilogram before one test, with 1 mg of chlorpromazine per kilogram before another test, and with isotonic saline (no drug) before two tests (*3*). Drug tests were alternated with no-drug tests. All injections were given intraperitoneally, between 15 and 60 minutes before the start of the test; this time-interval was within the effective range of the drugs. The drugs were dissolved in the same volume of isotonic saline (1 ml/kg) that comprised the no-drug injections. The rats were randomly assigned to one of four groups, which differed in the sequence of drug and no-drug tests. During each of the four test sessions one group was under caffeine, one group was under chlorpromazine, and two groups were under no drug. By these procedures, the order of drug conditions was counterbalanced, and each drug condition was tested in each session.

The tests were conducted in a circular observation cage 30 in. in diameter. Each male was given 2 minutes alone in the cage before the introduction into the cage of a female which was in full behavioral heat. The sexual behavior of male rats consists of mounting the female and making a brief intromission (copulation). On some occasions the male may mount without accomplishing an intromission. After a number of intromissions, generally between 10 and 20, ejaculation occurs. The male withdraws from the female and shows no sexual interest for at least 15 seconds after each intromission and for at least several minutes after ejaculation.

Table 1 shows these measures of sexual activity, presented in terms of (i) latency in seconds of first occurrence after introduction of the female; (ii) frequency of occurrence during the 15-minute test; (iii) percentage of group performing the response; and (iv) copulatory rate. Copulatory rate is the average number of copulations per minute to ejaculation (or, if no ejaculation occurs, from the first copulation to the end of the test). These measures and the procedures are more fully described elsewhere (*4*). As is shown in Table 1, caffeine decreased the latencies to mount, copulate, and ejaculate and increased the frequency and rate of copulation. Chlorpromazine had opposite effects on all these measures except latency to ejaculation. Of interest is the failure of both drugs to alter significantly the percentage of subjects which copulated or ejaculated.

In order to test for the effects of the drugs on subsequent no-drug sessions, the tests following administration of caffeine were compared with the tests following administration of chlorpromazine. An additional 15-minute no-drug test was given to animals whose last regular test was with one of the drugs, in order to complete this procedure. The animals made more than twice as many mounts and 24 percent more copulations during the no-drug session following administration of chlorpromazine than during the no-drug session following administration of caffeine. The difference in number of mounts is statistically significant ($p < 0.05$ by Wilcoxon matched-pairs rank test). There were no reliable differences in the other measures of sexual behavior. Since the time interval between sessions was ample to allow the drug effects to dissipate, these results apparently point to differences in behavior learned under the two drugs. A more strenuous sexual response may have been learned under chlorpromazine to over-

come the depressant effects of the drug.

The wide range in sexual potency of our subjects was in part the result of antecedent conditions to which they were subjected in an experiment by one of us (P. G. Z.) (*5*). After weaning, 11 of the rats had been reared under unfavorable conditions (that is, they had been given electric shock for approaching a receptive female and had been subsequently reared in isolation, or they had been reared entirely in isolation). Six rats had been reared under more favorable conditions (that is, they had been given no electric shock when they were with a receptive female and had been reared in cohabitation with other males or with females). In order to increase the number of subjects in testing the differential effects of previous sexual experience, eight pretest rats were added to this comparative study. These animals had been reared under the same conditions as the others (five under favorable conditions, three under unfavorable ones) but were given four *ten*-minute tests and were not given a no-drug test between the two drug tests.

In the various measures of sexual performance, the depressant effects of chlorpromazine were found to be approximately equal among animals reared under these two sets of conditions. On the other hand, the stimulating effects of caffeine were evident only among animals reared under the more favorable conditions. These animals copulated almost twice as many times when they were under caffeine as when they were under no drug and showed an increment, under caffeine, in number of mounts, in copulatory rate, and in percentage that copulated and ejaculated. Among the animals reared under unfavorable conditions, caffeine produced only a slight increment in copulatory rate and a slight decrement in all of these other measures. The effect of rearing conditions on the caffeine-versus-no-drug difference was statistically significant for number of copulations ($p < 0.02$) and almost significant for number of mounts ($p < 0.10$), according to the Mann-Whitney rank test. The different effects of caffeine might be explained by the hypothesis that the stimulating effects of caffeine enhance whatever behavior tendency is dominant in the situation. If the conditions of rearing have been favorable, positive sexual responses will generally be dominant; if the conditions of rearing have been unfavorable, inhibitory or incompatible responses may be dominant.

The study described in the present report confirms and extends the finding by Soulairac and Coppin-Monthillaud of the stimulating effect of caffeine on sexual behavior—even of a smaller dose. A depressant effect of chlorpromazine was also found. The use of non-drug tests and of animals with variation in previous sexual experience permitted further observations on effects of the drugs.

PHILIP G. ZIMBARDO
HERBERT BARRY, III
Department of Psychology, Yale University, New Haven, Connecticut

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23 September 1957

Electromigration on Filter Paper of Uric Acid from Serum and Synovial Fluid

It has long been a matter of discussion whether uric acid is present in human serum as a free molecule or is bound to other components such as proteins. Ultrafiltration and dialysis have given controversial results in this connection (*1*). Zone electrophoresis on filter paper offers a new approach to the study of the problem.

Previous reports from our laboratory (*2*) have shown that several techniques can be followed for identification and evaluation of uric acid on the strip of filter paper. The most practical technique proved to be direct treatment of the strip with silver nitrate and sodium lactate; uric acid appears, then, as a brown band on a white background. While this method is suitable for detecting the position of the spot of uric acid, quantitative data are more readily obtained by elution and chemical (*3*) or ultraviolet absorption analysis.

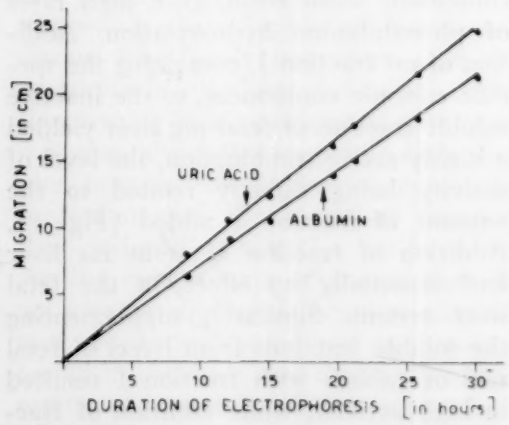

Fig. 1. Migration of serum uric acid and serum albumin as a function of duration of electrophoresis, in standard conditions of potential gradient (2.5 v/cm) and temperature (15°C), in Veronal at pH = 8.6, $\Gamma/2 = 0.05$. Each point represents an average of four experiments. In calculating distance of migration, it has been assumed that the starting point corresponds to the band of gamma globulin.

Paper electrophoresis was performed in accordance with the method of Durrum, as modified by Flynn and De Mayo (*4*). Different buffer solutions were tried: Veronal at pH = 8.6, $\Gamma/2 = 0.10$, 0.05, and 0.025, respectively; phosphate at pH = 7.2, $\Gamma/2 = 0.05$; acetate at pH = 5.4, $\Gamma/2 = 0.05$; glycine-NaOH at pH = 9.7, $\Gamma/2 = 0.05$. The best results, as far as resolution of protein components and uric acid is concerned, were obtained with Veronal buffer at pH = 8.6, $\Gamma/2 = 0.05$. Whatman No. 31 extra-thick filter paper was used.

Forty-two sera from normal subjects and from hyperuricemic patients with gout, nephritis, and leukemia and ten samples of synovial fluid from gouty and rheumatic subjects were studied. Control experiments were run with pure uric acid solutions of different concentration (from 3 to 20 mg percent). The results obtained can be summarized as follows:

1) Uric acid present in serum and synovial fluid showed the same electrophoretic behavior as uric acid in free solution, in all the conditions of pH, ionic strength, potential gradient, temperature, and duration of migration that were tried. A single band was always obtained for this substance. Though we cannot rule out entirely the possibility that there was a dissociation of labile bonds between uric acid and other serum components, it is not likely that such a dissociation would have occurred under the mild conditions of our experiments.

2) The mobility of uric acid, as judged from the electrophoretic migration on filter paper, proves to be slightly higher than that of serum albumin, being about 15 percent greater (Fig. 1).

3) No change of the electrophoretic behavior of uric acid was observed after general or intra-articular administration of drugs that are active in modifying uricemia (prednisone, phenylbutazone, probenecid, pyrazinamide).

Our results seem to indicate that uric acid is not bound to other serum components and is not present in a particular chemical form; several drugs that act on uric acid metabolism and excretion fail to modify the physical or chemical properties of this substance in the blood.

FRANCO SALTERI
ELISA CIRLA
ANGELO FASOLI
Institute of Clinical Medicine and Medical Therapy, University of Milan, Milan, Italy

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4 November 1957

Development of Phenylalanine Hydroxylase in Mammalian Liver

Recent studies of the mechanism of conversion of phenylalanine to tyrosine in the soluble fraction of liver homogenates have established that the reaction requires the participation of two discrete enzymes in addition to reduced pyridine nucleotide (*1, 2*) and an as yet unidentified cofactor (*3, 4*). One of the enzymes can be prepared from tissues that do not hydroxylate phenylalanine (for example, kidney, brain, spleen); this suggests that a reaction of more general nature is involved. The second enzyme, which is specific, has been found only in liver. Wallace *et al.* (*5*) and Mitoma *et al.* (*6*) have recently demonstrated that the livers of phenylketonuric individuals lack this specific enzyme, thus strengthening the prevailing concept regarding phenylketonuria—namely, that the syndrome is associated with a specific congenital inability to oxidize phenylalanine to tyrosine.

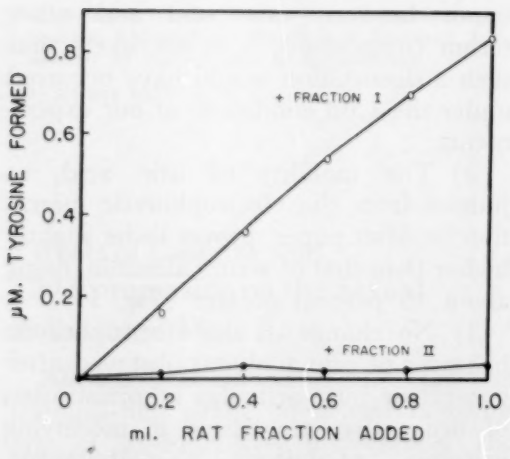

Fig. 1. Effect of rat liver fractions on phenylalanine hydroxylation in the liver of the fetal pig. Beakers containing 1.0 ml of the soluble fraction of fetal pig liver (17.2 mg of protein), 150 μmole of potassium phosphate buffer (*p*H 6.8), 2 μmole of DPNH, 2 μmole of L-phenylalanine, rat liver fractions as indicated, and 0.15*M* KCl to make a total volume of 3.0 ml were shaken for 60 minutes at 35°C. Tyrosine formed was measured colorimetrically. Rat fraction I, 3.3 mg of protein per milliliter; rat fraction II, 7.3 mg of protein per milliliter; these fractions individually formed only traces (less than 0.01 μmole) of tyrosine in 60 minutes.

Investigations on the development of this enzyme system in fetal, newborn, and adult rats have established the fact that the over-all reaction is virtually absent in fetal liver and in the livers of rats less than 24 hours old. In these experiments, 1.0 ml soluble fractions of liver (prepared from 33 percent homogenates in 0.15*M* KCl by centrifugation at 105,000*g* for 30 minutes) were shaken at 35°C for 60 minutes with 150 μmole of potassium phosphate buffer (*p*H 6.8), 2 μmole of L-phenylalanine, 2 μmole of reduced diphosphopyridine nucleotide (DPNH), and 5 μmole of nicotinamide in a total volume of 1.75 ml; the tyrosine formed was measured colorimetrically (*7*).

Under these conditions, preparations from adult animals and from animals 4 to 12 days of age converted all or most of the added phenylalanine to tyrosine, while preparations from fetal or newborn animals were essentially inactive. These inactive preparations could not be activated by substitution of TPNH (reduced triphosphopyridine nucleotide) for DPNH, or by increasing the amount of reduced pyridine nucleotide either by direct addition or by supplementing the reaction mixture with appropriate reducing systems (glucose-6-phosphate and yeast glucose-6-phosphate dehydrogenase with TPN; lactate and muscle lactic dehydrogenase with DPN). The ability to hydroxylate phenylalanine was also absent or negligible in livers of fetal pigs and fetal rabbits.

Experiments were carried out in order to determine which of the components is absent or inactive in fetal liver. Fractions I and II were prepared from adult rat livers by the procedure of Mitoma (*2*); each of these preparations alone was essentially inactive, while the two combined, when fresh, gave high rates of phenylalanine hydroxylation. Addition of rat fraction I, containing the specific enzymic component, to the inactive soluble fraction of fetal pig liver yielded a highly active combination, the level of activity being directly related to the amount of fraction I added (Fig. 1). Addition of fraction II from rat liver had essentially no effect on the fetal liver system. Similarly, supplementing the soluble fractions from livers of fetal rats or rabbits with fraction I resulted in high activity, while addition of fraction II was ineffective.

The absence of phenylalanine hydroxylation in fetal liver thus results from the same deficiency as that observed in the livers of patients with phenylpyruvic oligophrenia—that is, the specific enzymic component of the system, present in rat fraction I, is apparently not present in fetal liver.

Further, although fraction I has been described as being quite labile (*2*), it was found that aged or dialyzed preparations of this fraction, which were in fact inactive when assayed with fraction II, were still active in supplementing the fetal liver system. However, if the fetal liver preparation was well dialyzed, addition of aged or dialyzed fraction I was only slightly effective. These results indicate that fraction I contains two components, one of which is rapidly lost on aging or dialysis, and that this labile component is present in fetal liver. Loss of this component on dialysis, as well as on aging, suggests a factor of low molecular weight, which may be the auto-oxidizable cofactor described by Kaufman (*4*).

These findings lend support to the conclusion that the component missing in fetal liver, which is supplied by rat fraction I, is the specific hydroxylation enzyme. It is of interest to note that some other enzymes whose deficiency in postnatal life is associated with disorders of incomplete metabolism are also not active in fetal tissues; those investigated include the enzymes of tyrosine oxidation (*8*) and glucose-6-phosphatase (*9*). This relationship is being studied further in this laboratory (*10, 11*).

FRANCIS T. KENNEY
GABRIELLE H. REEM
NORMAN KRETCHMER

Department of Pediatrics, New York Hospital–Cornell Medical Center, New York

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10. Experiments similar to those described above were carried out with the soluble fractions of livers from two premature infants (liver samples obtained at autopsy, 9 and 2 hours after death). As with the fetal tissue, these preparations were inactive alone, active when rat fraction I was added, and not affected by rat fraction II. Although these results suggest that the liver of the premature infant also lacks the specific hydroxylation enzyme, the possibility exists that the time which elapsed between death and the enzyme assays was sufficient for specific autolysis of this enzyme.

11. These studies were supported in part by grants from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health (A-389 C3R); the Association for the Aid of Crippled Children; and the Damon Runyon Memorial Fund.

4 October 1957

Book Reviews

The Demand and Supply of Scientific Personnel. David M. Blank and George J. Stigler. National Bureau of Economic Research, New York, 1957. xix + 200 pp. $4.

In the preface of this book the authors explain what they have attempted to do: "The present monograph is primarily a study of the methods by which one can explain movements in the supply and demand for scientific personnel. Rather than discuss the problem in abstract terms, however, we have deemed it more fruitful to apply the methods under examination to the recent situation in the technological professions in the United States, that is, up to 1955." The result of this effort is a book with five chapters—"A General View of the Technological Professions," "Demand and Supply: Method of Analysis," "Factors Influencing the Demand for Engineers and Chemists," "The Supply of Engineers," and "Supply and Demand for Mathematicians and Physicists"—and eight appendixes, the most important of them being "(*A*) Engineering Earnings," "(*D*) Projection of the Number of Engineering Degrees to 1970," and "(*H*) The Engineers Joint Council Surveys."

After finishing the book, one may wonder if scientific personnel has been considered in its entirety and if the methods used really can explain movement in its supply and demand.

First, it seems that such a strict delimitation of the scientific personnel studies as was in fact used raises some inplications having a direct effect on the validity of the study. For instance, it does not seem possible to study the problem of scientific personnel in itself. That is to say, one cannot consider only the case of a particular category of scientific personnel (engineers, for example) apart from the other categories (technicians, foremen, and others) or consider solely the scientific personnel, apart from the administrative and commercial personnel, since there exist possibilities of moving from one category to the other.

Also, one would like to know more about "what is an engineer" and to know exactly what categories of people are under examination. The authors are talking about the census definition of an engineer (page 10 and pages 174–178), but one has to look at Appendix *B* (page 154) and Appendix *E* (page 174) in order to know what this definition is, and to page 11 for the standard requirements for membership in the professional engineering societies. These requirements are narrower than the census definition. With respect to the choice of the census definition, "less exacting than that of the professional engineering societies" (page 10) and including both graduate and nongraduate engineers, one may ask (i) if all people examined and grouped under the heading of "engineer" are performing approximately the same functions; (ii) if this is not too broad a definition; and (iii) if it would not have been better to examine only the graduate engineers. Two facts bear on these doubts about the validity of the methods used in this study. First, it is not possible to know the number of nongraduate engineers in each industry [the figures given for 1940 (page 11) and for 1950 (Appendix *F*) are not by sectors of industry but by number of years of professional training]; on page 69 the authors assume "that new entrants consist solely of engineering graduates with bachelor's degrees" and exclude in their forecast the losses of and the demand for nongraduate engineers. Moreover, the place of nongraduate engineers is studied in the "Supply of Engineers" (pages 86–92). It is evident that the authors saw all those difficulties, since they wrote, "it is surprising that so little is known about the ways in which they [the nongraduate engineers] enter the profession and the kinds of function they perform" (page 87), but in studying the nongraduate engineers they do not give us any supplementary information about them, and one is therefore forced to conclude that this study of the supply of and demand for engineers is only a partial one, not representing the entire situation.

Second, the method used does not appear to give a complete explanation of the phenomenon and raises the question of its suitability. For example, although the authors are "deeply interested in the economic questions implicit in an allegation of shortage" (page 23), they reject two meanings of the word *shortage* as it is applied to members of a particular profession—situations in which the actual number of available workers is less than the number dictated by some social criterion or goal or those in which the quantity of the labor services in question that is demanded is greater than the quantity supplied at the prevailing wage—and they adopt a third one: a shortage exists when the number of workers available (the supply) increases less rapidly than the number demanded at the salaries paid in the recent past (pages 23–24). And they add: "In any event, this is a well defined and significant meaning of the word 'shortage' and we propose to investigate now whether such a shortage has existed for engineers in recent decades" (page 24).

It seems clear that, in the minds of the authors, money was, is, and will be the only explanation for the demand and supply of engineers—and, therefore, for their shortage or surplus. And all engineers were, are, and will be pure calculating "*homines economici*" since "the differentials of engineers' earnings above those of the academically untrained labor force are still in excess of the costs of obtaining an engineering degree . . ." (page 31) and, "in principle, one would expect occupational choice to be largely determined by the discounted values of expected life earnings in alternative occupations, compared with the discounted costs of entering these occupations" (page 79). This psychology of the "*homo economicus*" has been attacked by economists for a long time—Veblen played an important part in this attack at the turn of the century—and cannot pretend to explain the behavior of a human being. It is more than doubtful that wages can explain the movements of supply and demand for the past eighty years. What is rather surprising is that the authors seem not to be completely persuaded of the validity of their only means of explanation, since they write: "For lack of data, we cannot discuss in detail the degree of future attractiveness (financial *or* otherwise) [italics supplied] of engineering as compared with other occupations that college graduates engage in" (page 75), and, "it would be desirable, we repeat, to examine the determinants of occupational choice among college students, but we shall not enter upon this large subject here. But it should be emphasized that the roles of income, stability of employment, subsequent breadth of choice of industry or type of work, and similar factors have not yet been examined quantitatively" (page 77). Therefore, earnings are not the only explanation of movements of supply and demand, and the conclusion about the

shortage of engineers has to be revised.

Again, even if this study is concerned with the situation and forecast of the number of engineers in the United States, the methods of predicting demand used by the U.S. Bureau of Labor Statistics and the Engineers Joint Council are not the only ones in use, and it seems unfortunate that no mention is made of the English and German methods of forecasting. Sometimes, some help can come from the other side of the Atlantic.

The explanation of the movements of the supply of, and demand for, scientific personnel in the past and forecast of these movements for the future remain to be made.

J. WOLFF
Commissariat Général à la Productivité, Paris, France

A Treatise on Limnology. vol. I. *Geography, Physics and Chemistry.* George Evelyn Hutchinson. Wiley, New York; Chapman & Hall, London, 1957. xiv + 1015 pp. Illus. $19.50.

Sixteen years ago teachers of hydrobiology refreshed their dog-eared limnology lecture notes when Hutchinson's mimeographed "Lecture Notes on Limnology" were made available in limited supply. Hopefully we have awaited the completion of the then envisioned *Treatise*. We were unanimously confident of the excellence and scholarly depth it would represent, and, now that the first of the two volumes is published, we are not disillusioned. Moreover, the biologists among us await eagerly the appearance of volume II on biology. Volume I is a masterly presentation and truly unique; a "monumental work," as it was so appropriately designated by a prepublication critic.

One might expect a *Handbuch* of these dimensions to be padded. This is not the case; it is packed with important and thoughtfully selected data. It is replete with examples drawn from all corners of the earth and with data assembled from some obscure "*Berichte*," "*Undersökningar*," "*Trudy (URSS)*," or "*Tôhoku*."

In this book scientists of many disciplines should find much that is required reading. I find a great deal of evidence to support the author's statement in the preface: "The book is addressed to all who are professionally concerned with limnology, but also to biologists who may wish to know something of the physiochemical environment, mode of life, and evolutionary significance of such freshwater organisms as they may study from quite different points of view; to geologists who are desirous of learning something of modern lakes in order that they may better interpret the record of inland waters in past times; and to oceanographers who wish to compare the results of their own science with what has been learned of the small but very individual bodies of water which make up the nonmarine part of the hydrosphere." To the latter clause I might add that the oceanographer, after reading this book, most certainly will be convinced of the usefulness of lakes as possible sites for experimental, small-scale oceanographic research. This is an opportunity they have not exploited.

As a thoughtful synthesizer of knowledge, Hutchinson is unsurpassed. Numerous instances bear this out, in which published and even unpublished data, from widely different sources, have been reworked to describe a new principle or to make an old one more clear. Readers of "Marginalia" in the *Sigma Xi Quarterly* must certainly have admired the great breadth of Hutchinson's reading and his literary skill. Occasionally one was "snowed under" by complex concepts expressed in elliptical style. In volume I of *A Treatise in Limnology* he has made every effort to explain clearly. In his "Lecture Notes on Limnology," the term *thermocline* was defined as "the horizontal plane defined by the inflection point of a temperature curve." In the *Treatise,* the definition now reads simply "the plane in which the temperature falls most rapidly." This should not be construed to mean that volume I is free from complex concepts, for to include such concepts is inescapable and to omit them would be undesirable. Many principles of physical limnology are involved and will be understood principally by those oceanographers and hydrobiologists whose training in mathematics, physics, and chemistry is adequate. One marvels at Hutchinson's versatility and at his ability to grapple competently with so many phases of science.

The following are some helpful features of the *Treatise*: (i) In the section on geological origin of lakes there is a concise summary of 76 lake types. (ii) A list of mathematical symbols is given, and an effort has been made to avoid duplications. (iii) An index of the lakes mentioned in the text gives the precise longitude and latitude of the location of each lake. (iv) A list of the genera and species that are discussed is given, together with a helpful listing of the taxonomic position of individuals in the plant and animal kingdoms. (v) There are 1489 references. Asterisks identify the titles of works of unusual limnological interest and those with extensive lists of references. (vi) Tables on the inorganic ions in rain, lakes, and rivers present data nowhere else available in one place. (vii) A concise summary concludes each chapter.

For publisher should be praised for his interest in publishing a professional volume of this kind. There is justification here for some type of subsidy, because the many students and field-station staff-members who could best profit from this book will be unable to afford it.

The book is embellished here and there by a witty comment, a fitting quotation from the classics, or even by a light verse. For example:

> "Big swirls have little swirls
> That prey on their velocity,
> And little swirls have lesser swirls
> And so on . . . to viscosity."

ARTHUR D. HASLER
University of Wisconsin

Géologie Sédimentaire. Les séries marines. Augustin Lombard. Masson, Paris; Vaillant-Carmanne, Liége, 1956. 722 pp. Illus. F. 11,000.

The field of sedimentary geology can, if the definition is broad enough, include almost all facets of geology except petrology of the igneous rocks. To include all aspects of this generalized subject in one volume is an almost impossible task. Lombard has amassed an amazing amount of information in a well-organized volume which includes 13 plates, 180 illustrations, and 34 pages of bibliography. Inevitably in such a broad subject some of the sections are little more than brief outlines, and in some cases these brief outlines are not as comprehensive as they should be. In part I the general subject of recent marine sediments, topography, and structure of the ocean basins is treated in too brief a manner, and several important references are omitted; for example, Emery, Tracey and Ladd on coral reefs and flat-topped seamounts [*U.S. Geol. Survey Profess. Paper No. 260-A* (1954)]; Phleger, Parker, and Peirson on present-day planktonic Foraminifera [*Reports of the Swedish Deep-Sea Expedition No. 7* (1953)]; Revelle on pelagic sediments [*Carnegie Inst. Wash. Publ. No. 556* (1944), pt. 1]. In part II the analysis of sediments does not include the Wentworth reference so commonly used for clastic size classification in the United States [*J. Geol.* 30, 382 (1922)]. In part 3 the writer gets into his special field of stratigraphy and produces an excellent and well-documented discussion of such difficult subjects as facies and rhythmic deposits.

All in all, Lombard has produced a valuable addition to the knowledge of sedimentation and stratigraphy, especially of the European section. American geologists will find the bibliography especially helpful because of the numerous references to European journals.

E. L. HAMILTON
San Diego, California

Colorimetric Analysis. vol. I, *Determinations of Clinical and Biochemical Significance*. Noel L. Allport and J. W. Keyser. Chapman & Hall, London, ed. 2, 1957 (order from Macmillan, New York). 424 pp. Illus. $9.

Two changes may be immediately noted in this new edition: a junior author (Keyser) has been added, and there are to be two volumes. This volume has been limited to methods used in clinical and biochemical analysis for substances occurring in body fluids and tissues.

The substances selected total 98, of which 82 are organic. The inorganic substances include the cations Ca^{++}, Cu^{++}, Fe^{+3}, H^{+}, Hg^{++}, K^{+}, Mg^{++}, Na^{+}, Pb^{++}, and Zn^{++} and the anions Br^{-}, I^{-}, PO_4^{-3}, SO_4^{--}, SiO_3^{--}, and SCN^{-}. In a number of cases, such as that of hemoglobin, there are several procedures. All of them seem to have been selected on the basis of ease of manipulation and reasonable reliability. Whether the selection is the best possible could be answered only by one familiar with all such methods. Many other methods are cited in references, mostly to biochemical sources, at the end of each section. Also, an appendix lists references, and principles of the methods, for 32 organic substances of biochemical interest which are not described in the text.

For each constituent there is usually a very brief statement of the principle involved in the production of the colored system to be measured. These sections might well be expanded. Next comes a concise, "cook-book" type of statement of the operating technique, including preparation of necessary reagents. The discussion that follows deals with the possibilities and limitations of the method.

There is some divergence in nomenclature from the preferred usage of *Chemical Abstracts*. Examples are *silicofluoride* (*fluosilicate*), *arsenomolybdic* (*molybdoarsenic*), and *α-α′-dipyridyl* (*2,2′-bipyridine*). In general, the book seems to have been carefully done.

M. G. MELLON
Purdue University

Microwave Measurements. Edward L. Ginzton. McGraw-Hill, New York, 1957. xvii + 515 pp. Illus. $12.

This is an excellent reference book, of professional quality, devoted to microwave measurements. The author was a colleague of the late W. W. Hansen, with whom initial plans for the book were made. Ginzton can claim technical proficiency in this field in his own right, and I mention this fact merely to point out that I feel that there is no less need for such a book now than there was when this one was originally planned, probably soon after World War II.

The author intended this book to be a useful reference volume for those who have more than a routine interest in microwave measurement problems. He has succeeded in this aim, and it is for this reason that I would classify this as a professional reference book. There is general continuity in treatment of the material, so that, unlike a handbook, this book can be used for graduate courses in microwave measurements.

The author assumes that the reader has competence in electromagnetic theory, and he uses what theory he gives in the text itself merely for the justification of certain concepts—for example, the impedance concept. By assuming this initial familiarity with the field, the author is able to delve quite deeply and rapidly into the topics he has decided to cover. Being thus able to deal immediately with the details of the apparatus and the methods used in microwave measurements, Ginzton is able to consider in most cases the quantitative description of the devices and methods used. In other instances he at least discusses qualitatively the operation of the devices.

As can be inferred from the above remarks, this book is not a "cookbook" of recipes for making microwave measurements. Proper attention is given to the basic theory as well as to the apparatus or method being employed. There are, however, in the book explicit and detailed instructions for carrying out the actual measurement operation. For example, in the section referring to the making of standing-wave-ratio measurements with slotted lines, Ginzton discusses the many pitfalls of the method with the tender and loving care of a man who has made measurements himself and who has possibly, at some time in the dim distant past, encountered the very pitfalls he is warning about now. A feature of format which warrants favorable mention is the use of footnotes to develop simple algebraic relationships or proofs referred to in the text. To develop these proofs for himself would frequently demand considerable ingenuity on the part of the reader, and the necessity for doing so would often be annoying. Having them available along with the text is of definite advantage. The topics covered in the book are of broad general interest. The absence of some specialized topics in microwave measurements—for example, measurements in microwave spectroscopy—is no great loss. The topics discussed are generation, detection, and measurement of microwave power; the concept of, and the measurement of, microwave impedances; and the representation of microwave radiation. The book ends with a discussion of the measurement of cavities and of their Q_0 and their R_0/Q_0, or electric field distribution and, finally, of the measurement of attenuation.

The book is well illustrated with line drawings, photographs, and graphs, and the material is documented with an extensive and very useful bibliography.

An obvious attempt has been made to make the material as up-to-date as possible. However, material of transient or specialized interest has not been considered; hence, the material in the book will probably become obsolete very slowly. In a book such as this, where a large number of techniques are covered, there is bound to be a variation in the excellence with which the material is presented. Although all sections of the book demonstrate professional competence, only certain sections are truly authoritative. For example, the chapter on the measurement of wavelength is very well done, while the chapter on the measurement of frequency is adequate but uninspired. I would even quibble about the selection of some of the material—for example, the ammonia maser is discussed from the point of view of a frequency standard, and the cesium beam is not even mentioned.

These are trivial complaints on the whole, and, in summary, the book must be considered as a worth-while contribution to the literature on the microwave field and, especially, as an excellent reference book on microwave measurements.

M. W. P. STRANDBERG
Research Laboratory of Electronics, Massachusetts Institute of Technology

Gas Dynamics. Klaus Oswatitsch. English version by Gustav Kuerti. Academic Press, New York, 1956. 610 pp. Illus. + charts. $12.

This volume is an excellent treatment of modern gas dynamics, covering the material usually presented in a first-year graduate course in compressible flow theory. It begins with an introduction to the basic thermodynamic relations and quantities, following which the steady one-dimensional flow of a gas in a duct of varying cross section is considered. Brief introductions to normal shock waves and to the effects of energy addition and friction are included. Next follows a chapter on unsteady one-dimensional flow in ducts of constant cross section and with no friction or energy release. The theory of characteristics is introduced and applied to various special solutions. The interaction of shocks and shock waves in cylindrical and spherical coordinates is also considered.

The next three chapters deal with the fundamental relations for two- and three-dimensional steady flow. Integral theo-

rems are established, Prandtl-Meyer flow is presented, and the hodograph and other transformations are introduced. There follows a chapter on steady, ideal, plane, and axisymmetric subsonic flow. This chapter contains a detailed treatment of linearized theory, the Prandtl-Glauert rule, and the methods of Rayleigh-Janzen and Karman-Tsien. Numerical relaxation methods are treated briefly.

The next chapter deals with steady, ideal, plane, and axisymmetric supersonic flow. Linearized theory is presented, followed by consideration of the oblique shock and applications of the method of characteristics to nonlinear isentropic flow. Specific applications are given to airfoils, nozzles, jets, cascades, and bodies of revolution at incidence. There is a brief discussion of hypersonic flow. The next chapters deal with transonic flow and with miscellaneous unsteady multidimensional flow situations. There is a brief chapter summarizing some of the more important results for compressible boundary layers, laminar and turbulent jets, separation, stability, and shock-wave thickness.

The volume closes with a survey of some of the more standard experimental techniques. There are no exercises. The bibliography is somewhat brief. There are brief tables and charts for the dynamic relations of various gases.

SAMUEL A. SCHAAF
University of California, Berkeley

The North American Deserts. Edmund C. Jaeger. Stanford University Press, Stanford, 1957. x + 308 pp. Illus. $5.95.

Edmund C. Jaeger, curator of plants at the Riverside Municipal Museum, is a student of desert ecology, acquainted with animals as well as plants. He is also a competent expositor and illustrator, whose knowledge and talents have been put to effective use in what adds up to a very convenient guidebook to the deserts of North America. Peveril Meigs has provided a good chapter on desert weather and climate, and the author acknowledges generous assistance from numerous other collaborators.

After a general discussion on deserts and the chapter by Meigs, five great desert areas—the Chihuahuan, Sonoran, and Mohave deserts, the Great Basin, and the Painted Desert—are described. The account of one of them, the Sonoran, is broken up into six subdivisions. Physical conditions, flora, fauna, and human cultures are dealt with in a manner that should be appreciated by professional worker and layman alike; both popular and scientific names are given for all organisms. Helpful travel hints are also included. This portion of the book is well illustrated with maps and photographs.

It is followed by some 130 pages of plates and brief descriptions of desert insects, reptiles, birds, mammals, and plants, by a page on the euphonious Spanish names, so indispensable in the Southwest, and by a good index.

Apart from their intrinsic interest and beauty and the growing pressure to convert them into something "useful," deserts are becoming of increasing interest from a scientific standpoint. In Inner Mongolia, Spain, and our own Southwest, the sediments of former lakes are revealing records of climatic change extending back through the Pleistocene and beyond, giving a continuity not possible within the glaciated region itself. Scientists who will, in increasing numbers, be engaged in such studies owe a debt of gratitude to Jaeger and his collaborators, since the desert is not likely to be a familiar environment to many of them.

PAUL B. SEARS
Conservation Program,
Yale University

New Books

Artificial Stimulation of Rain. Proceedings of the first Conference on the Physics of Cloud and Precipitation Particles. Held at Woods Hole Oceanographic Institution, Woods Hole, Mass., 7–10 Sept. 1955. Pergamon Press, New York and London, 1957. 443 pp. $15.

Forest Fertilization. A bibliography, with abstracts, on the use of fertilizers and soil amendments in forestry. Compiled by Donald P. White and Albert L. Leaf. State University College of Forestry, Syracuse University, Syracuse, N.Y., 1957. 303 pp. $3.

Instinctive Behavior. The development of a modern concept. Translated and edited by Claire H. Schiller. International Universities Press, New York, 1957. 347 pp. $7.50.

No and Yes. On the genesis of human communication. Rene A. Spitz. International Universities Press, New York, 1957. 182 pp. $4.

Surgery in World War II. Ophthalmology and *Otolaryngology.* John Boyd Coates, Jr., Ed. Medical Department, U.S. Army, Washington, 1957 (order from Supt. of Documents, GPO, Washington 25). 628 pp. $5.

Manual of Microbiological Methods. Society of American Bacteriologists, Committee on Bacteriological Technic. McGraw-Hill, New York, 1957. 325 pp. $5.50.

Deafness, Mutism and Mental Deficiency in Children. Louis Minski. Philosophical Library, New York, 1957. 90 pp.

The Volunteers. Means and ends in a national organization. David L. Sills. Free Press, Glencoe, Ill., 1957. 340 pp. $6.

Human Histology. A textbook in outline form. Leslie Brainerd Arey. Saunders, Philadelphia, 1957. 346 pp.

Atomic Power, an Appraisal. Including atomic energy in economic development. Corbin Allardice, Ed. Pergamon Press, New York and London, 1957. 151 pp. $3.50.

Cytochemical Methods with Quantitative Aims. Biophysical and biochemical approaches. Experimental Cell Research, Supplement 4, 1957. Proceedings of the symposium, 27–29 Sept. 1956, Institute for Medical Cell Research and Genetics, Karolinska Institutet, Stockholm, Sweden. Academic Press, New York, 1957. 296 pp. $9.50.

Miscellaneous Publications

(Inquiries concerning these publications should be addressed, not to Science, *but to the publisher or agency sponsoring the publication.)*

Federal Funds for Science. VI. The Federal Research and Development Budget, Fiscal Years 1956, 1957, and 1958. National Science Foundation, Washington, 1957 (order from Supt. of Documents, GPO, Washington 25). 60 pp. $0.40.

Education Associations. Part 4 of Education Directory 1956–57. Office of Education, U.S. Department of Health, Education, and Welfare, Washington 1957 (order from Supt. of Documents, GPO, Washington 25). 79 pp. $0.30.

American Museum of Natural History, Eighty-Eighth Annual Report, July 1956–June 1957. The Museum, New York, 1957. 77 pp.

The Age of Space. Proceedings of a nontechnical conference on missiles, rockets, and space travel—and their impact on our times. 16 May 1957. Southern Research Institute, Birmingham, Ala., 1957. 43 pp.

Scientific Resources of the San Francisco Bay Area. International Science Foundation, Golden Gate Park, San Francisco, 1957. 96 pp. $5.

Hydrography of the Faroe-Shetland Channel, 1927–1952. Scottish Home Department, Marien Research, 1957, No. 2. John B. Tait. Her Majesty's Stationery Office, Edinburgh, 1957. 309 pp. £5 5s.

Enuresis. A clinical and genetic study (*Acta Psychiat. et Neurol. Scand.*, vol. 32, Suppl. No. 114). Bertil Hallgren. Munksgaard, Copenhagen, Denmark, 1957. 159 pp.

Étude Théorique des Oscillations Libres (Seiches) du Lac Tanganika. Exploration hydrobiologique du Lac Tanganika, 1946–1947. vol. II, fasc. 3, *Resultats Scientifiques.* F. Servais. Institut Royal des Sciences Naturelles de Belgique, Bruxelles, 1957. 311 pp.

Inventions Wanted by the Armed Forces. U.S. Department of Commerce. National Inventors Council, Washington 25, 1957. 34 pp.

Polemoniacae of Nevada. Edgar T. Wherry. *Ipomopsis and Gilia Sect. Arachninon* contributed by Verne Grant and Alva Grant. Contributions toward a Flora of Nevada, No. 43. Plant Industry Station, Beltsville, Md., 1957. 103 pp.

Ecological Life History of the Warmouth (Centrarchidae). Survey Bulletin, vol. 27, art. 1. R. Weldon Larimore. Illinois, Natural History Division, Urbana, 1957. 84 pp.

Meetings and Societies

Tektites

The growing scientific interest in cosmology and the relation of cosmic matter to the genesis of the elements has focused attention on all available samples of extraterrestrial matter. Inasmuch as meteorites are frequently seen to fall, their extraterrestrial origin is certain. Another class of objects, the tektites, may also be extraterrestrial, even though none has ever been observed to fall.

The tektites are glass objects that are found in several widely separated places on the earth (southern Australia, Texas, Czechoslovakia, the Philippine Islands, Java, the Ivory Coast, and the Libyan Desert). In each area many individual specimens, which weigh from 0.1 to 1000 grams each, have been found. They are often symmetrical in shape, and, in the case of the australites, their shapes are distinctly suggestive of "flow patterns." In bulk chemical composition they differ from obsidian and other volcanic extrusive rocks but resemble certain sedimentary rocks. That they cannot be of volcanic origin is shown by their distribution in areas where there is no associated volcanism. They are not associated with known meteorite craters, and they differ from the glassy "impactite" from such craters in their homogeneity and in the fact that they do not include nonfused local rocks. They all seem to be associated with sedimentary formations of Eocene to Pleistocene age.

Workers in the late 1890's proposed that these objects are of extraterrestrial origin. If this is so, tektites represent samples of cosmic matter different from that of the stony and iron meteorites. Even if they should be strictly terrestrial, their shapes, distribution, and occurrence pose problems of considerable interest.

The possibility of learning something more about the nature and origin of tektites by application of modern techniques has resulted in research on tektites by people in widely separated disciplines, including astrophysics, geology, geochemistry, and nuclear science. It was felt by some of these workers that a conference that would bring together a large group of persons actually engaged in tektite research, as well as other scientists who might be able to contribute to the various problems they pose, would be very useful. Accordingly, the Earth Sciences Division of the National Academy of Sciences–National Research Council requested and obtained support from the National Science Foundation for this purpose.

The Conference on Problems of Tektites was held at the National Academy of Sciences–National Research Council building in Washington, D.C., 17–18 June. Twenty scientists participated, and Irving Friedman served as chairman. Although several foreign scientists were invited, F. G. Houtermans, of Berne, Switzerland, was the only one able to be present. E. L. Krinov, of Moscow, sent a paper which was read at the conference, as were two lengthy letters from H. Otley Beyer, of Manila.

Technical discussion. The sessions started with the presentation of a paper, "Tektite localities in the United States," by Virgil E. Barnes (University of Texas), who summarized much of the present knowledge of tektites and their distribution. The only well-established occurrence in the United States is near a 120-mile length of the tilted sedimentary rocks of the Jackson formation, of late Eocene age, which crops out along a northeast-southwest line through Texas. Here the tektites seem to be eroding out of the Jackson formation, whose stratigraphic age is about 35 million years. A few specimens from Georgia suggest, but are insufficient to establish, an occurrence there. All other reported occurrences in the United States are now attributed to obsidian. The "americanites" of Colombia and Peru are also believed to be obsidian. Barnes favors a meteoritic origin for tektites; because of the close similarity of their chemical composition to that of terrestrial sedimentary rocks, he feels that similar rocks on another planet, later disrupted, might be the source of the material.

The hypothesis of a disrupted planet is also favored by William A. Cassidy (Pennsylvania State University), who reported on phase equilibrium investigations on tektites. He emphasized the double analogy between granites and tektites on the one hand and between mafic terrestrial rocks and stony meteorites on the other. He also noted that a recently discovered region of two-liquid immiscibility in molten mixtures of SiO_2, Al_2O_3, K_2O, and FeO corresponds to the gap in silicon content separating the tektites (more than 70 percent SiO_2) from the stony meteorites (less than 60 percent SiO_2). This suggests a differentiation between silicate groups with gravitational stratification in the parent planet, which would then have consisted of a metallic core, a crystalline mantle of mafic silicates, and an outer layer of sialic character. The latter may have been kept molten by its high concentration of radioactive elements up to the time of disruption, at which time the liquid presumably solidified into particles and the various sizes and shapes were caused by rotation. The surface features of those particles found on earth were caused by superficial heating during entry into the atmosphere.

Support for the meteoritic nature of tektites was given by studies of cosmic-ray-induced radioactivities in meteorites and tektites, reported by William D. Ehmann and Truman P. Kohman (Carnegie Institute of Technology). They found Al^{26} (half-life about one million years) in australites at about the same level as in chondritic meteorites, whereas this nuclide was absent in moldavites (Czechoslovakian tektites), in bediasites (Texas tektites), and in the terrestrial materials examined. This checks with the very fresh appearance of australites and indicates intervals, since fall, of at least several million years for moldavites and bediasites, which are highly weathered. A lower but definite level of Al^{26} in Libyan Desert silica-glass indicates that this material is to be classified as tektitic and meteoritic and that it fell about four million years ago. The occurrence of Be^{10} (half-life 2.7 million years) in some meteorites and tektites was indicated, but the levels of occurrence and the absence of Be^{10} in terrestrial materials were less well established.

The extreme unlikelihood that a swarm of particles could keep together in interplanetary space in such a way as to strike the earth in areas as small as the observed tektite-strewn fields was emphasized by Fred L. Whipple (Smithsonian Astrophysical Observatory). Whipple presented a paper, with Carlos Varsovsky, titled "Dynamical limits on a lunar origin for tektites." Certain considerations suggest that the collision of a large meteorite with the moon might eject molten matter in a right-circular hollow cone of rather narrow wall thickness, and that if this cone strikes the earth, its thickness might be reduced by a focusing effect of the earth's gravitational field. Calculations, now being programmed for the M.I.T.-I.B.M. computer, of orbits of particles leaving the moon from various points with various initial directions and velocities, may establish the validity or lack of validity of the "lunar impactite" hypothesis. Whipple also presented valuable summaries of present knowledge and theories concerning comets and meteors. Any connection between tektites

and either of these classes of objects seems quite unlikely to him.

The assumption that tektites are formed from terrestrial materials was supported by several of the participants. A paper submitted by Krinov (scientific secretary of the Committee on Meteorites of the Academy of Sciences of the U.S.S.R.), entitled "Some considerations on tektites," was read. The findings of Soviet and other investigators seem to Krinov to support Spencer's theory that tektites are high-velocity impactites that were formed as a result of collisions of large meteorites with the earth. A paper, "Origin of Tektites" [*Nature* **179**, 556 (1957)], was submitted by H. C. Urey (University of Chicago) and read by the chairman. This paper described possible effects of collision of the head of a comet with the earth, which might include the fusing and scattering of terrestrial rock as tektites. Dynamics of collisions of large meteorites with the earth's surface were considered in detail by John S. Rinehart (Smithsonian Astrophysical Observatory) on the basis of controlled impact experiments and theory. His paper, "Impact effects and tektites," developed a mechanism by which the forms of tektites could result from the impact of a large crater-forming meteorite.

Several speakers presented information on various aspects of the physical and chemical composition of tektites. Alvin J. Cohen (Mellon Institute) described absorption spectra of tektites and showed that the principal light absorption feature is due to ferrous iron. No radiation effects were observed, evidently because of a built-in "radiation protection" mechanism. In contrast to tektites, most obsidians show water absorption bands and radiation-induced absorption. F. G. Houtermans (Physikalisches Institut, Berne, Switzerland) reported on studies of thermoluminescence of meteorites. Both chondrites and tektites show stored radiation-induced thermoluminescence, though in the case of tektites the irradiation is not necessarily attributable to cosmic rays because there is a fairly high content of radioelements.

Quantitative data on the content of radioelements in tektites were given by several speakers. John A. S. Adams (Rice Institute) reported extensively on the thorium and uranium contents of tektites. Most tektites have between 1 and 2 parts of uranium per million and have thorium-uranium ratios of about 7 to 1. Libyan Desert silica-glass has somewhat less than 1 part of uranium per million, whereas americanite has more than 18 parts per million. Similar results were obtained by Friedman (U.S. Geological Survey), whose paper is mentioned below. Adams found that most tektites have about 2.5 percent potassium. William H. Pinson (Massachusetts Institute of Technology) and Leonard F. Herzog (Pennsylvania State University) showed in their paper, also mentioned below, that the potassium and rubidium contents of tektites are remarkably constant at about 2.5 percent and 0.01 percent, respectively.

Friedman's paper, titled "Water, gas, and uranium content of some tektites," indicated that tektites have low water content, in contrast to other characteristics that indicate similarity to obsidians. Most tektites have between 20 and 100 parts of water per million whereas obsidians have from 800 to 3500 parts per million. The Libyan glass has somewhat higher water content (more than 700 ppm) and moldavites considerably lower (3 to 5 ppm) than the other tektites. Hydrogen and other noncondensable gases are lacking. The deuterium-hydrogen ratio of the tektite waters is in the range of that of terrestrial waters. The indications are that tektites were melted in the absence of water (this supports the assumption that they are of nonterrestrial origin) or were heated to a temperature in excess of 2000°C in a terrestrial environment.

Various age determination methods involving radioactivity are being applied to tektites. H. E. Suess (Scripps Oceanographic Institute) reviewed the potassium-argon work, which has given upper age limits of several million years. It may be possible to date the solidification of tektites as glass by this method. More sensitive methods now available might give actual values rather than limits for this age for various tektites. Pinson and Herzog, whose paper was titled "Rubidium-strontium ages of tektites," observed rather uniform radiogenic strontium-87 abundance in several tektites. Because the proportion of radiogenic strontium-87 to total strontium-87 is very small, the rubidium-strontium ages are highly uncertain and are very sensitive to the model chosen for the reservoir material from which the tektite specimen separated. For example, if the material of tektites was fractionated from average terrestrial material, their ages would be about 400 ± 200 million years. (Work done since the conference has revealed a systematic error in the strontium isotope results reported. Strontium-87/strontium-86 ratios in eight tektite samples from widely scattered localities are nearly identical, and equal to the ratio found in present day "common" strontium. The rubidium-strontium ages of all samples are thus in the range 10 ± 75 million years; in agreement with potassium-argon age data.) The isotopic composition of lead from tektites was discussed by George Tilton (Carnegie Institution of Washington). The lead from an australite was found to be almost identical with average modern terrestrial lead and totally unlike any meteorite lead.

Publication plans. The majority of the papers presented at the conference will be published in one issue of *Geochimica et Cosmochimica Acta,* to appear probably early in 1958.

General recommendations. H. Otley Beyer (University of the Philippines, Manila), in a letter to the chairman of the conference, pointed out that it is often difficult to learn the names and addresses of people currently engaged in tektite research. As a result, the conference approved his suggestion that a directory of those actively interested in tektites be compiled. It is expected that this directory will facilitate exchange of ideas, reprints, and specimens. All interested persons should write to E. P. Henderson, U.S. National Museum, Smithsonian Institution, Washington 25, D.C., describing their current work on, and interest in, tektites.

The conference chairman suggested that, in view of the difficulty most workers experience in obtaining specimens of tektites, a central clearinghouse for specimens be established to help serious students obtain material for their experimental work. The Smithsonian Institution is being asked to act as agent in these transactions. Several of those present felt that their respective institutions would be willing to subscribe funds for the purchase of specimens for this purpose, and it is hoped that a small research collection may be built up with such funds at the Smithsonian Institution. Through this arrangement experimental material could be used to full advantage, since several experiments can often be run on the same specimen if the sequence is "programmed" correctly. Those interested in obtaining tektite material for their work should write to E. P. Henderson, describing their needs and stating whether or not they could reimburse the institution or offer material in exchange.

Comments. The conference showed that definite progress is being made in solving some of the problems presented by tektites. However, the key problem—whether these objects are of cosmic or terrestrial origin—is not settled. Their chemical composition, the isotopic composition of their lead, and the difficulty of explaining their distribution on astronomical grounds make a terrestrial origin seem likely. On the other hand, their cosmic-ray-induced radioactivity, their low water content, and the difficulty of explaining their distribution on geological grounds make a cosmic origin seem equally likely.

Many of those present felt compelled to pursue further their investigations on tektites or to initiate work along new lines. In writing this report, we feel justified in stressing several avenues of investigation that seem particularly promising for future work.

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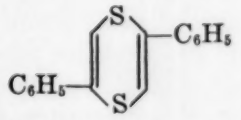

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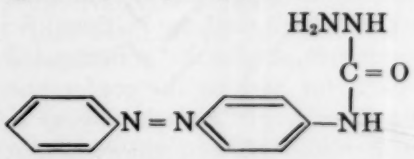

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Additional and more intensive field work on the occurrences of tektites would be valuable. Only in the case of the Libyan Desert silica-glass does the true size and shape of the strewn field appear to be known. Recoveries of material from the ocean bottom off southern Australia, in the Southeast Asia area, and off the Ivory Coast of Africa seem to be possible and would be of great interest. Any possible connection between the Libyan glass field and a group of craters, possibly of impact origin, some hundred kilometers south of the area of the glass field should be investigated.

Laboratory investigations of phase separations in cooling silicate melts of low water-content should be continued and extended to include the effects of pressure.

In connection with studies of cosmic-ray-induced radioactivity in tektites, much more extensive examination of terrestrial materials is needed to determine exactly what their rate of production is at the earth's surface as a function of altitude and geomagnetic latitude. In this connection, in addition to location, the altitude and probable amount of past overburden should be noted and recorded for all meteorites and tektites that are collected.

Various methods of determining age should be applied, with maximum possible sensitivity and precision, to as many occurrences of tektites as possible. Knowledge of the times of the different processes dated by the different approaches may help in understanding their history. Several specimens from each occurrence should be examined, to determine the extent of homogeneity or possible variability.

Quantitative astronomical studies of the behavior of swarms of particles in space should be extended to all possible conditions. Efforts should be made to learn more about the nature of the lunar surface and, in particular, to deduce or, preferably, physically sample its chemical composition.

The main result of the conference was to focus attention on tektite problems and to bring them to the attention of a wider group of scientists. The National Academy of Sciences, the National Research Council, and the National Science Foundation are to be commended and thanked for making the conference possible. It is hoped that in a year or two another conference of more international scope can be arranged.

IRVING FRIEDMAN
U.S. Geological Survey, Washington, D.C.

TRUMAN P. KOHMAN
Carnegie Institute of Technology, Pittsburgh, Pennsylvania

WILLIAM A. CASSIDY
Pennsylvania State University, University Park, Pennsylvania

Society Elections

■ American Society of Parasitologists: pres., Arthur C. Walton, Knox College; pres.-elect, Aurel O. Foster, U.S. Department of Agriculture; vice pres., Raymond M. Cable, Purdue University; sec., Paul E. Thompson, Parke, Davis & Co.; treas., Robert M. Stabler, Colorado College.

■ American Chemical Society: pres.-elect for 1959, John C. Bailar, Jr., University of Illinois; pres. 1958, Clifford F. Rassweiler, Johns-Manville Corp.

Regional directors reelected are: Wallace R. Brode, National Bureau of Standards, and William G. Young, University of California.

■ Medical Library Association: pres., Thomas E. Keys, Mayo Clinic Library; pres.-elect., Isabelle T. Anderson, Denver Medical Society Library; sec., Henrietta T. Perkins, Yale Medical Library; treas., Pauline Duffield, Texas Medical Association Library.

Forthcoming Events

February

1–14. Pan American Assoc. of Ophthalmology, Caribbean cruise cong., sailing from New York, N.Y. (L. V. Arnold, 33 Washington Sq. W., New York 11.)

3–4. Progress and Trends in Chemical and Petroleum Instrumentation, Wilmington, Del. (H. S. Kindler, Instrument Soc. of America, 313 Sixth Ave., Pittsburgh 22, Pa.)

3–7. American Inst. of Electrical Engineers, winter genl., New York, N.Y. (N. S. Hibshman, AIEE, 33 W. 39 St., New York 18.)

5–7. Biophysical Soc., Cambridge, Mass. (A. K. Solomon, Biophysical Lab., Harvard Medical School, Boston, Mass.)

10–14. American Soc. for Testing Materials, St. Louis, Mo. (F. F. Van Atta, ASTM, 1916 Race St., Philadelphia 3, Pa.)

13–15. National Soc. of Professional Engineers, spring, East Lansing, Mich. (NSPE, 2029 K St., NW, Washington 6.)

16–20. American Inst. of Mining, Metallurgical and Petroleum Engineers, annual, New York. (E. O. Kirkendall, AIME, 29 W. 39 St., New York 18.)

20–21. Transistor and Solid State Circuits Conf., Philadelphia, Pa. (J. H. Milligan, Jr., Dept. of Electrical Engr., New York Univ., New York 53.)

22–25. American Educational Research Assoc., St. Louis, Mo. (F. W. Hubbard, AERA, 1201 16th St., NW, Washington 6.)

24–28. American Soc. of Civil Engineers, Chicago, Ill. (W. W. Wisely, ASCE, 33 W. 39 St., New York 18.)

March

1. Junior Solar Symposium, Tempe, Ariz. (Association for Applied Solar Energy, 3424 N. Central Ave., Phoenix, Ariz.)

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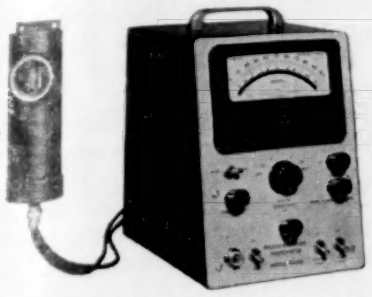

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1515 Mass. Ave., NW, Washington 5, D.C.

1–3. National Wildlife Federation, St. Louis, Mo. (E. F. Swift, NWF, 232 Carroll St., NW, Washington 12.)

3. Wildlife Soc., annual, St. Louis, Mo. (D. L. Leedy, U.S. Fish and Wildlife Service, Washington 25.)

5–6. Gas Conditioning Conf., 7th annual, Norman, Okla. (M. L. Powers, Extension Div., Univ. of Oklahoma, Norman.)

6–8. Fundamental Cancer Research, 12th annual, Houston, Tex. (W. K. Sinclair, M. D. Anderson Hospital and Tumor Inst., Univ. of Texas, Houston 25.)

6–8. Optical Soc. of America, annual, New York. (A. C. Hardy, Massachusetts Inst. of Technology, Cambridge 39.)

10–13. American Assoc. of Petroleum Geologists, annual, Los Angeles, Calif. (R. H. Dott, AAPG, Box 979, Tulsa 1, Okla.)

10–13. Society of Economic Paleontologists and Mineralogists, annual, Los Angeles, Calif. (R. H. Dott, Box 979, Tulsa, Okla.)

16–21. Nuclear Engineering and Science Cong., Chicago, Ill. (D. I. Cooper, *Nucleonics,* 330 W. 42 St., New York.)

17–21. National Assoc. of Corrosion Engineers, 14th annual, San Francisco, Calif. (NACE, Southern Standard Bldg., Houston 2, Tex.)

18–20. Amino Acids and Peptides, Ciba Foundation symp. (by invitation), London, England. (G. E. W. Wolstenholme, 41 Portland Pl., London, W.1.)

20–22. Michigan Acad. of Science, Arts and Letters, annual, Ann Arbor. (R. F. Haugh, Dept. of English, Univ. of Michigan, Ann Arbor.)

20–22. Pulmonary Circulation Conf., Chicago, Ill. (Wright Adams, Chicago Heart Assoc., 69 W. Washington St., Chicago 2.)

20–23. International Assoc. for Dental Research, annual, Detroit, Mich. (D. Y. Burrill, Univ. of Louisville, School of Dentistry, 129 E. Broadway, Louisville 2, Ky.)

23–26. American Assoc. of Dental Schools, annual, Detroit, Mich. (M. W. McCrea, 42 S. Greene St., Baltimore 1, Md.)

23–29. American Soc. of Photogrammetry, 24th annual, jointly with American Corg. on Surveying and Mapping, 18th annual, Washington, D.C. (C. E. Palmer, ASP, 1515 Massachusetts Ave., NW, Washington 5.)

24–27. Institute of Radio Engineers, natl. conv., New York. (G. W. Bailey, IRE, 1 E. 79 St., New York 21.)

27–29. National Science Teachers Assoc., 6th natl., Denver, Colo. (R. H. Carleton, NSTA, 1201 16 St., NW, Washington 6.)

29. South Carolina Acad. of Science, annual, Charleston. (Miss M. Hess, Dept. of Biology, Winthrop College, Clemson, S.C.)

29–30. American Psychosomatic Soc., 15th annual, Cincinnati, Ohio. (T. Lidz, 551 Madison Ave., New York 22.)

30–3. American College Personnel Assoc., annual, St. Louis, Mo. (L. Riggs, DePauw Univ., Greencastle, Ind.)

April

1–3. Corrosion Control, 5th annual conf., Norman, Okla. (M. L. Powers, Ex-

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tension Div., Univ. of Oklahoma, Norman.)

2–4. American Assoc. of Anatomists, annual, Buffalo, N.Y. (L. B. Flexner, Dept. of Anatomy, School of Medicine, Univ. of Pennsylvania, Philadelphia 4.)

2–4. Instruments and Regulators Conf., Newark, Del. (W. E. Vannah, Control Engineering, 330 W. 42 St., New York 36.)

4–5. Southern Soc. for Philosophy and Psychology, annual, Nashville, Tenn. (W. B. Webb, U.S. Naval School of Aviation Medicine, Pensacola, Fla.)

7–11. American Assoc. of Cereal Chemists, annual, Cincinnati, Ohio. (J. W. Pence, Western Utilization Research Laboratories, Albany, Calif.)

8–10. Electronic Waveguides Symp., New York. (J. Fox, Microwave Research Inst., Polytechnic Inst. of Brooklyn, 55 Johnson St., Brooklyn 1, N.Y.)

9–12. National Council of Teachers of Mathematics, Cleveland, Ohio. (M. H. Ahrendt, NCTM, 1201 16 St., NW, Washington 6.)

9–14. Applied Psychology, 13th internatl. cong., Rome, Italy. (L. Meschieri, National Inst. of Psychology, Rome.)

10–11. American Inst. of Chemists, annual, Los Angeles, Calif. (L. Van Doren, AIC, 60 E. 42 St., New York 17.)

10–12. National Speleological Soc., annual, Gatlinburg, Tenn. (G. W. Moore, Geology Dept., Yale Univ., New Haven, Conn.)

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10–12. Ohio Acad. of Science, annual, Akron, Ohio. (G. W. Burns, Dept. of Botany, Ohio Wesleyan Univ., Delaware, Ohio.)

11. Vitamin B-12 Symp., New York, N.Y. (Miss J. Watson, 451 Clarkson Ave., Brooklyn 3, N.Y.)

11–12. Eastern Psychological Assoc., annual, Philadelphia, Pa. (G. Lane, Dept. of Psychology, University of Delaware, Newark.)

11–18. Horticultural Cong., 15th internatl., Nice, France. (Secretariat General, 84, rue de Grenelle, Paris 7e, France.)

13–14. American Soc. for Artificial Internal Organs, Philadelphia, Pa. (G. Schreiner, Georgetown Univ. Hospital, Washington 7.)

13–18. American Chemical Soc., 133rd, San Francisco, Calif. (R. M. Warren, ACS, 1155 16 St., NW, Washington 6.)

13–19. Federation of American Societies for Experimental Biology, annual, Philadelphia, Pa. (M. O. Lee, FASEB, 9650 Wisconsin Ave., Bethesda 14, Md.)

14–16. Automatic Techniques Conf., Detroit, Mich. (J. E. Eiselein, RCA, Bldg. 10–7, Camden 2, N.J.)

14–18. American Assoc. of Immunologists, annual, Philadelphia, Pa. (F. S. Cheever, Graduate School of Public Health, Univ. of Pittsburgh, Pittsburgh 13, Pa.)

14–18. American Soc. for Experimental Biology, annual, Philadelphia, Pa. (J. F. A. McManus, Univ. of Alabama Medical Center, Birmingham.)

14–18. American Soc. of Biological Chemists, annual, Philadelphia, Pa. (P. Handler, Dept. of Biochemistry, Duke Univ. School of Medicine, Durham, N.C.)

15–17. Gas Measurement, 34th annual conf., Norman, Okla. (M. L. Powers, Extension Div., Univ. of Oklahoma, Norman.)

17–19. Association of Southeastern Biologists, annual, Tallahassee, Fla. (J. C. Dickinson, Jr., Dept. of Biology, Univ. of Florida, Gainesville.)

18. Iowa Acad. of Science, annual, Des Moines. (C. H. Lindahl, Dept. of Mathematics, Iowa State College, Ames.)

18–19. Arkansas Acad. of Science, annual, Little Rock. (L. F. Bailey, Botany Dept., Univ. of Arkansas, Fayetteville.)

19–21. American College of Apothecaries, Los Angeles, Calif. (R. E. Abrams, Hamilton Court, 39th and Chestnut St., Philadelphia, Pa.)

20–22. American Assoc. of Colleges of Pharmacy, annual, Los Angeles, Calif. (G. L. Webster, College of Pharmacy, Univ. of Illinois, 808 S. Wood St., Chicago 12.)

20–23. Chemical Engineering Conf., Canada-United States, Montreal, Quebec. (H. R. L. Streight, DuPont Company of Canada, P.O. Box 660, Montreal.)

21–23. American Oil Chemists' Soc., Memphis, Tenn. (Mrs. L. R. Hawkins, AOCS, 35 E. Wacker Dr., Chicago 1, Ill.)

21–28. American Industrial Hygiene Assoc., annual, Atlantic City, N.J. (G. D. Clayton, George D. Clayton and Associates, 14125 Prevost, Detroit 27, Mich.)

22–24. Electronic Components Symp., Los Angeles, Calif. (E. E. Brewer, Convair, Inc., Pomona, Calif.)

(See issue of 20 December for comprehensive list)

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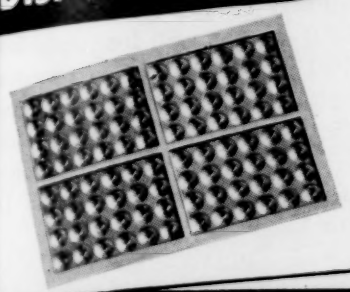

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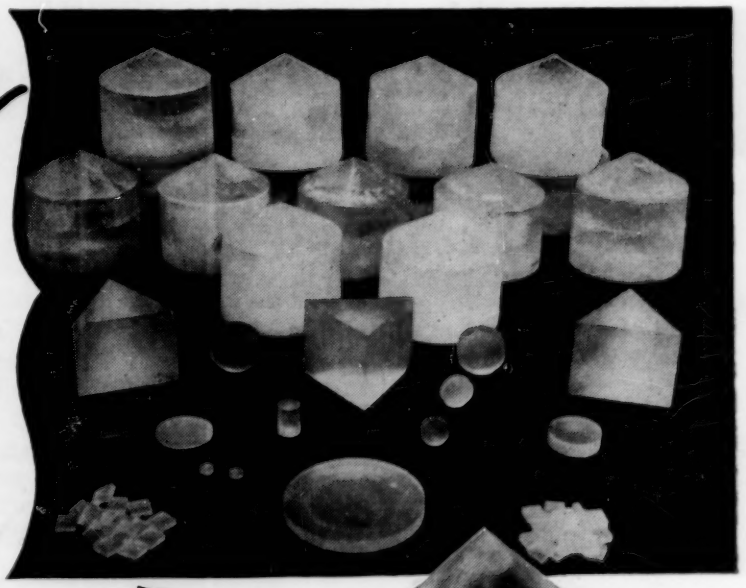

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